VOLUME 86 NUMBER 2

ARCHIVES
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INTERNAL MEDICINE

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AUGUST 1950

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A METHOD OF IMPROVING FUNCTION OF THE BOWEL

J. ARNOLD BARGEN, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

Any diet for relief of constipation must supply material which has limited absorption in the small intestines and which adds bulk in the colon, i.e., fruits and vegetables. Daily fluid intake, from 2.5 to 3.5 liters, is highly important. Since many people find it difficult to eat enough dietary bulk, the trend recently has been toward hydrophilous colloids.

A search was made for such a colloid, for oral use, which has little or no effect in the stomach and small intestines. Methylcellulose, appropriately prepared as Cellothyl tablets, seems to answer these criteria.

A large number of patients received 4 tablets every 4 hours, with subsequent relief of constipation. These patients had no ordinary form of constipation; they had taken quantities, or as some said, "barrels of laxatives." In the following cases of obstinate constipation of long duration, a striking change for the better followed the use of this preparation, as part of a program of general medical care:

RESULTS OF TREATMENT

Case 1. Woman, age 57.—Obstinate constipation since early childhood. *After treatment:* Complete relief. She continued to pass normal, soft formed stools.

Case 2. Nun, age 69.—Obstinate constipation of lifelong duration. *After treatment:* In about a week . . . soft stools.

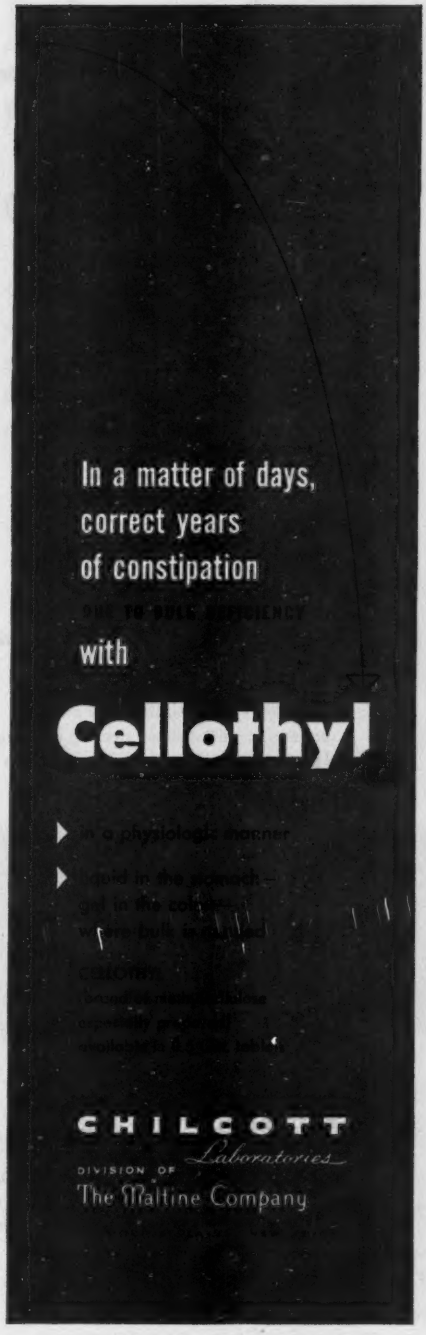
Case 3. Man, age 44.—Constipated many years; severe diabetes. *After treatment:* Normal stools at the end of one week.

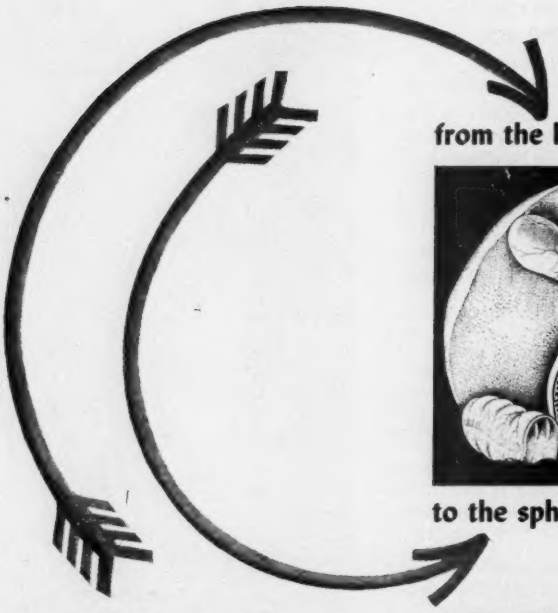
Case 4. Woman, age 62.—Very difficult evacuation after carcinoma removal. *After treatment:* She passed her stools without discomfort.

Case 5. Woman, age 19.—Obstinate constipation; she had taken a laxative almost daily since early childhood. *After treatment:* At the end of two weeks she was passing stools daily.

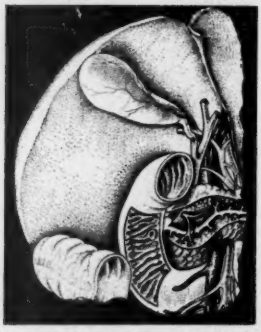
COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared (Cellothyl). It represents a valuable addition to the well-ordered program of medical care.





from the liver parenchyma



to the sphincter of Oddi

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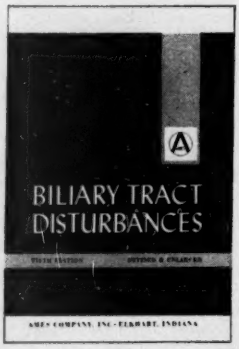

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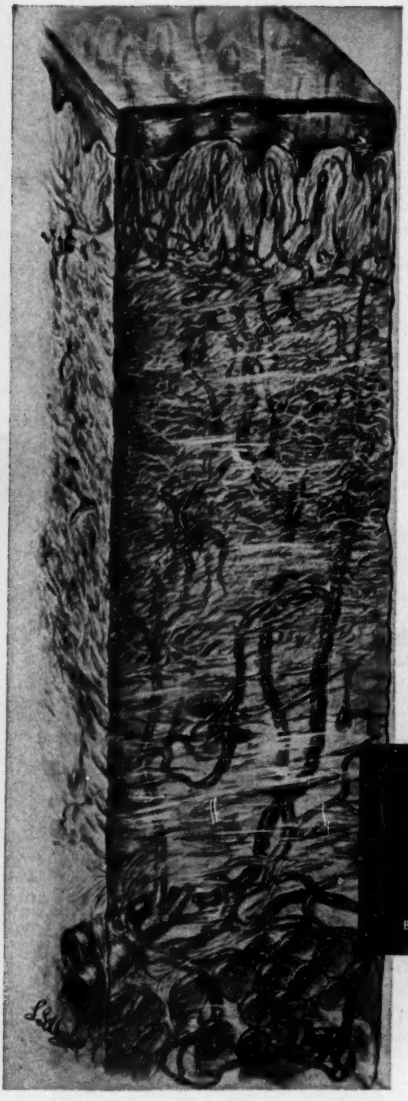

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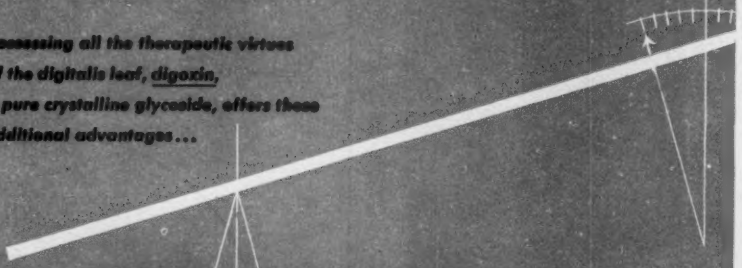

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ARCHIVES of INTERNAL MEDICINE

VOLUME 86 AUGUST 1950 NUMBER 2

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LETTER FROM THE EDITORIAL BOARD

Since the close of World War II the American literature of the specialty of internal medicine has undergone major changes. Several new periodicals representing subspecialties within the field have been started. Others presenting material of interest to all internists in new and interesting form are also establishing themselves in the libraries of medical schools, hospitals and physicians' offices. Obviously no single publication in the field of internal medicine can contain all the reports of importance and no physician can hope to read and digest all the excellent material in the many specialty journals now available to him. Both readers and authors are confronted with the problem of which periodicals are best suited to their needs.

At a recent meeting of the Editorial Board of the ARCHIVES OF INTERNAL MEDICINE the question of possible changes in editorial policy to keep pace with changes both in trends of research and in trends of reader interest was thoroughly explored. After considerable discussion, it was decided that the original statement of policy of the first Editorial Board of the ARCHIVES still presented the major objectives of the present incumbents as clearly as could be set down. This statement was published as an announcement by the Editorial Board of 1907,[1] which included Dr. Joseph L. Miller, Dr. George Dock, Dr. W. S. Thayer, Dr. David L. Edsall, Dr. Theodore Janeway and Dr. Richard Cabot:

> The Board of Trustees of the American Medical Association has taken steps for the founding of the *Archives of Internal Medicine*. It will be devoted to the publication of original studies on clinical medicine carried out at the bedside or in the laboratory, and of physiological, pathological and pharmacological researches that have a bearing on the nature, diagnosis or treatment of disease. Scholarly, thorough work, well abreast of the present position of medical science, is what is desired for the *Archives of Internal Medicine*. All technical details and protocols necessary to prove the thesis will be welcome, although unnecessary details are to be avoided. Articles that summarize what is already known on a certain topic and then add something new, represent the class of communications that are desired, as well as short original communications on matters relating to internal medicine.

Within a few months the ARCHIVES, in company with other publications of the American Medical Association, will appear in a new and attractive format. There may be minor changes in content such as

1. J. A. M. A. **49**:1790 (Nov. 23) 1907.

the addition of editorials on matters of current interest. However, in the selection of articles the requirements will continue to be honest, scholarly reports of the type that will help the internist at the bedside, in the classroom and in the pursuit of new knowledge in the laboratory. The Editorial Board looks back with regret on the large number of rejected manuscripts of the past few years, most of which contained interesting and informative material but which were returned to the authors because of their bulk, their lack of originality or their lack of conclusiveness in the experimental data. The Board views with satisfaction, however, the many new concepts and discoveries first presented in the pages of the ARCHIVES and the repeatedly quoted authoritative data contained in the papers of its distinguished contributors. The Board proposes to keep its standards high and, barring unforeseen misfortunes such as the prolonged printers' strike which resulted in irregular publication for more than a year, it intends to keep the stockpile low enough that articles submitted to the ARCHIVES may clear through its Editorial Board and be published within four months of their receipt at the American Medical Association offices.

ARTHUR BLOOMFIELD, M.D.
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PAUL S. RHOADS, M.D., Chief Editor.

DIAGNOSTIC PROBLEMS IN JAUNDICE

FRANKLIN M. HANGER, M.D.
Professor of Medicine, Columbia University College of Physicians and Surgeons
NEW YORK

IN THE ABSENCE of excessive hemolysis, an increase of bile pigments in the blood or tissues indicates some type of abnormality at the "hepatocellular barrier," i. e., the aggregations of hepatic and reticuloendothelial elements that separate the blood-containing sinusoids from the bile capillaries. Bilirubin, on which the color of bile depends, is an iron-free derivative of hemoglobin formed by the action of reticuloendothelial cells at the site of the breakdown of red blood cells that is constantly taking place within the body. In its initial state the pigment "hemobilirubin" or "bilirubinglobin" is firmly conjugated with globin or with an albumin-like constituent of the serum complex. This bilirubin-protein compound is not excreted by the kidney and fails to give a prompt direct color reaction with Ehrlich reagent. It is, however, readily removed from the blood by the liver, so that levels between 0.1 and 1 mg. per hundred cubic centimeters are maintained with remarkable constancy in the normal subject.

The mechanisms involved in the transfer of bilirubin from blood and from the Kupffer cells to the biliary system are not clear, since the pigment cannot ordinarily be visualized or demonstrated in transit across the hepatocellular barrier. Observations on the excretion by the liver of fluorescent dyes, such as fluorescein, or of radioactive sulfobromophthalein (bromsulphalein®) sodium indicated, however, that certain materials conjugated with the serum proteins are removed selectively from the blood by the polygonal cells without the mediation of the Kupffer cell system, and transfer is effected as the material in solution becomes more concentrated in the bile capillaries. These studies suggested that not only selective excretion but controlled reabsorption of fluid takes place at the surface of the hepatic cells bounding the intralobular biliary channels.

The uptake from the blood of hemobilirubin, its transformation to the more diffusible, direct-reacting bilirubinate and the maintenance of selective excretion involve, no doubt, integrated enzymatic activities of the hepatic cells; but the directing forces are unknown by which not only bile pigments but other constituents of bile, such as cholic acid derivatives, cholesterol and alkaline phosphatase, are transferred toward

the biliary spaces while other metabolites, such as urea, glucose, cholesterol esters and proteins, are transmitted in an opposite direction toward the blood stream (see figure).

Disorders of the hepatic cells may lead to jaundice by a variety of mechanisms. With extensive parenchymal destruction it is obvious that the hepatocellular barrier is no longer effective and that the contents of the bile channels may spill back into the spaces of Disse and thence by way of the lymphatics into the blood stream. More speculation is required to explain hepatogenous jaundice when necrosis of the hepatic cells is not demonstrable and the hepatocellular barrier appears intact. In some cases injured, but seemingly viable, parenchymal cells are

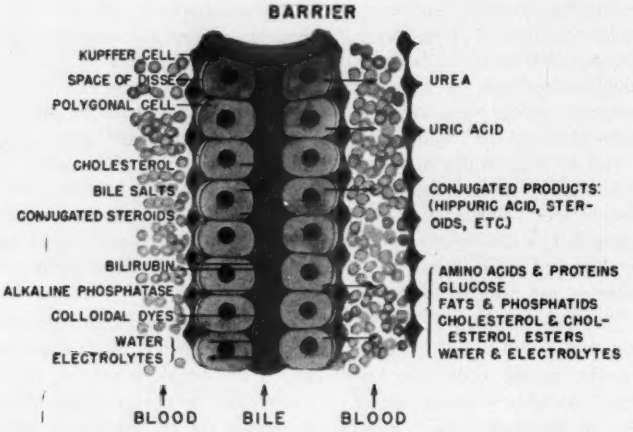

Diagram of hepatocellular barrier indicates barrier of hepatic tissues separating the vascular and biliary systems. Arrows indicate the directional orientation by the hepatic cells of substances excreted with the bile and those transferred into the blood.

observed deeply stained with bile pigments, as though there were intrinsic difficulties in maintaining effective physiologic transport of the pigment across the cell, or perhaps indicating resorption of bile by the injured cell from the bile capillaries, with a reversal of excretory flow from bile spaces back to the blood.

EFFECT OF BILIRUBIN DISTURBANCES

The conversion of delayed indirect-reacting bilirubin to the prompt direct-reacting form is probably accomplished not only by the pigment traversing the hepatocellular barrier but by mere exposure of hemobilirubin to the enzymatic action of the hepatic cells. For example, the

deep jaundice of acute massive necrosis of the liver is due largely to the presence of prompt direct-reacting bilirubin which increases rapidly in the blood at a time autolyzing debris is abundant but few viable cells remain in the liver and the formation of bile in the biliary system has practically ceased. Some authorities attributed to the Kupffer cells the conversion of hemobilirubin to bilirubinate, but there is little evidence for this assumption. These cells, like others of the reticuloendothelial system, convert hemoglobin to bilirubin, which in turn is excreted by the parenchymal cells. It must be pointed out that the differentiation between the serum bilirubin fraction giving a prompt direct reaction with Ehrlich reagent and the fraction giving a delayed or indirect reaction is an arbitrary one, since the physicochemical differences between the two depend in part on a time factor and on a number of variables in the serum complex. The question is often raised whether differences in the Ehrlich reaction justify the conventional concept of an irreversible transformation of bilirubin by the liver in the process of excretion. Notwithstanding theoretic reservations, the differentiation of the two fractions is of established clinical value in the study of the jaundiced patient.

Bile-stained casts in the terminal bile capillaries are commonly observed in the liver during jaundice. Undoubtedly, stasis is an important factor in the formation of these structures when biliary obstruction is present, but abnormal concentration and desiccation of bile due to excessive reabsorption of water by diseased hepatic cells must also be considered as a possible mechanism for decreasing the quantity of bile and its pressure of flow. Suffice it to say that bile plugs probably do not actually cause jaundice, but their presence is indicative of derangements leading to faulty excretion of bilirubin.

Many types of injury to the cells of the liver disturb the physiologic excretion of bilirubin. Important among these are certain viruses, toxic agents, anoxia, dietary deficiencies, excessive infiltration with fat or glycogen and inflammatory reactions. In various clinical situations more than one of these deleterious factors is implicated. For example, swelling of the cells may occlude the flow of bile by pressure on small biliary channels, causing superimposed obstructive jaundice. Likewise, in acute carbon tetrachloride poisoning the swelling of the injured hepatic cells, according to Himsworth, causes such narrowing of the sinusoids that anoxia adds to the hepatic damage, especially in the central portions of the lobule.

RETENTION JAUNDICE

Abnormalities of the hepatocellular barrier may cause jaundice by failure to clear the blood of hemobilirubin at the usual physiologic level. In these circumstances no bile is detected in the urine and the serum contains only delayed indirect-reacting bilirubin. This condition is usually regarded as a functional derangement, as it may be familial and is

unassociated with any abnormality of the liver demonstrable by histologic examination or by a large assortment of tests, save for delay in excretion of parenterally administered bilirubin. Excessive formation of bilirubin from increased destruction of blood (hemolytic jaundice) can be differentiated from retention jaundice by hematologic studies and by the determination that total stercobilin excretion is within normal limits. Physiologic hyperbilirubinemia occurs in 2 to 3 per cent of the general population. It gives rise to few symptoms except perhaps fatigability and nervous instability, which may be provoked in part by apprehensive parents and physicians. The bilirubinemia is seldom marked, and jaundice may become noticeable only after fatigue, physical exertion, intercurrent infections and other conditions causing accelerated breakdown of blood cells.

On the other hand, retention jaundice may accompany or follow infectious hepatitis and in some cases may be the sole residual mark of the disease. Various other types of hepatic and reticuloendothelial injury may also cause a rise in the excretory threshold of bilirubin. Indeed, an increase of hemobilirubin in the blood is usually found in jaundice of both the obstructive and the hepatogenous types. A searching history, many months of observation and repeated hepatic function tests, and even liver biopsy, may be necessary to evaluate the significance of retention jaundice in certain patients. It seems probable that most patients who acquire this symptom after having had hepatitis had latent or unrecognized physiologic hyperbilirubinemia before the infection. Practically none of the persons observed in my clinic with this complaint has shown any indication of progressive inflammatory or sclerosing disease. Certainly the coexistence of prompt direct-reacting bilirubin in the blood or bilirubinuria is much more suggestive of a grave hepatic disorder.

BILIARY OBSTRUCTION

The factor of biliary obstruction must be considered in every case of jaundice, since its presence is often indicative of serious extrahepatic conditions requiring surgical correction. The mechanisms underlying obstructive jaundice can be adequately explained by numerous clinical and experimental studies. The liver excretes about 500 cc. of bile a day, which represents, no doubt, the concentrate of many times this amount of original fluid. Excretion can be maintained against a resistance of 100 to 200 mm. of water, but when the intrabiliary pressure exceeds about 300 mm. of water production of bile ceases. Obstruction leads to dilatation and rupture of the intralobular and perilobular bile channels, which then communicate with the spaces of Disse and with the lymphatics of the liver. Through these channels all the constituents of bile, such as bilirubin, bile salts and alkaline phosphatase, eventually gain entrance to the blood stream, where they may be demonstrated in increasing

amounts. Itching and bradycardia are common symptoms of obstructive jaundice and are usually attributed to elevation of bile salts in the blood. The level of bile salts, however, is maintained by both the rate of excretion of the kidneys and the rate of synthesis of the hepatic cells. It is common clinical experience that obstructive jaundice may cause but little itching when extensive parenchymal damage depresses the capacity for synthesis of bile salts by the liver. Bilirubin also is excreted readily by the kidneys, and so the appearance of dark urine is often of greater early clinical significance than the appearance of jaundice. Alkaline phosphatase, however, is not eliminated by way of the urinary tract in the human being; the determination of this enzyme in the serum is, therefore, an important test by which the factor of obstruction can be recognized in complex hepatic problems with or without jaundice. Biliary obstruction leads eventually to damage and selective impairment of function of the parenchymal cells. The injury is slow to develop, however, and a large number of important metabolic activities of the liver are maintained for many months in the presence of obstructive jaundice, unless other damaging factors, such as infection or neoplastic invasion, are associated with the process.

Numerous studies may be employed to differentiate hepatogenous jaundice from jaundice due to biliary obstruction. Diseases of the hepatic parenchyma sufficiently severe to give rise to jaundice usually cause enough impairment of metabolic activity to be detected by routine tests, such as delayed removal of galactose from the blood, increased urobilinogen in the urine or drop in the esterified cholesterol fraction in the blood below 70 per cent of the total. In most instances of hepatogenous jaundice, also, the degenerative and inflammatory changes in the liver give rise to qualitative alterations in the serum albumin fraction, which are detectable by a positive cephalin flocculation reaction, or to abnormal serum globulin complexes, as shown by the reactions to the thymol turbidity test and to many other tests for readily precipitable proteins. Conversely, uncomplicated obstructive jaundice gives rise to no abnormal serum protein reactions and metabolic activities of the liver are relatively well maintained, but certain metabolites normally excreted in the bile, such as alkaline phosphatase, tend to accumulate in the blood. It is, therefore, possible in about 90 per cent of all cases of jaundice to recognize the disturbing mechanism by correlating the clinical features through a preliminary screening with the following tests: (1) Calculation of the total serum bilirubin concentration, with determination of the immediate direct-reacting fraction, (2) the cephalin flocculation and thymol turbidity tests to detect active parenchymal damage and inflammatory changes and (3) the serum alkaline phosphatase determination to discover obstructive factors. A large number of metabolic studies is available, but these are seldom necessary in the initial screening or in

clearcut cases. Reactions to these tests are especially useful in complex clinical problems; they may be quite selective and often wide discrepancies are demonstrated among them, differences which depend in part on the nature and extent of the hepatic disorder.

DIFFERENTIAL DIAGNOSIS

Limitations in diagnosis by the employment of a few selected tests, such as the ones previously proposed, are due to the complexities of many of the disease processes of the liver. For example, although the lesions of infectious hepatitis are usually diffuse, instances occur in which damage is confined to only parts of the hepatic unit, such as the Kupffer system, parenchyma of the liver, perilobular spaces or portal triads. When the parenchyma is not involved in this disease, the cephalin flocculation reaction tends to be negative and intrahepatic lesions would be missed if too much dependence were placed on this test. In other instances of hepatitis with diffuse lesions reactions to the screening tests may indicate that the jaundice present is due to both parenchymal damage and biliary disturbance, but a number of unrelated conditions may give identical test results.

Added difficulties are caused by the limitations of the tests employed. Not all types of hepatic injury invoke changes in the serum proteins detectable by flocculation or turbidity tests. Hepatocellular jaundice with negative flocculation reactions may be seen in cases with fatty or hyaline degenerative changes in the hepatic cells, chronic passive congestion, compression by tumor masses and chronic anoxia. As a rule, when active dissolution of parenchymal cells or intralobular inflammatory infiltrations are present, a positive reaction can be expected, but it is not always possible by histologic examination to determine the result of the flocculation reaction. Furthermore, not all positive cephalin flocculation reactions indicate hepatic derangement. Certain diseases of the spleen and of the reticuloendothelial cells, such as infectious mononucleosis, may give rise to abnormal globulins in the serum which cause positive reactions by a different mechanism from that observed in hepatitis and cirrhosis.

Likewise, serum alkaline phosphatase levels may be misleading. Normal values are sometimes observed with acute obstructive jaundice and also rarely in cases of chronic obstruction in elderly or debilitated subjects. Furthermore, since alkaline phosphatase is supposedly derived in large part from osteoblasts, various disorders of the osseous system may cause either abnormal increases or abnormal decreases of the enzyme in the blood, irrespective of the status of the liver.

The following nonsurgical conditions with jaundice are notably difficult to differentiate by clinical or laboratory tests from diseases

requiring surgical management: (1) cholangitis and pericholangitis, (2) toxic degeneration of the liver and (3) infiltrations of the liver by neoplasms or granulomas.

DISEASE OF THE BILE DUCTS

Cholangitis, pericholangitis and cholangiolitis may be caused by virus infections or by sensitization of the ducts to drugs, as arsphenamine and cinchopen, or perhaps the inflammatory reactions in the biliary tissues, like arthritis or nephritis, may be a manifestation of focal or systemic infection elsewhere in the body. Cholangitis also is frequently secondary to stasis, obstruction and ascending infections in the common bile duct and its branches. When inflammation, edema or scarring is confined to the biliary radicles or to the supporting structures of the liver, such as the tissues of the portal triads, the picture is quite indistinguishable from that of extrahepatic obstructive jaundice. Often the metabolic functions of the liver, as galactose tolerance or synthesis of cholesterol ester, show more impairment when the obstructive process is intrahepatic, but it is hazardous to differentiate extrahepatic from intrahepatic jaundice by the reactions to these tests. Surgical visualization of the entire liver and biliary tract, rather than a needle biopsy, is indicated in all cases of persisting or increasing jaundice accompanied with a negative cephalin flocculation reaction, by a negative result of the thymol turbidity test and by elevation in serum alkaline phosphatase. This dictum leads to an occasional futile surgical procedure; however, the ruling out of possible new growths, calculi or stricture of the bile ducts and the establishment of the type of lesion within the liver well justify the procedure. Furthermore, patients with intrahepatic obstruction usually stand operation well and often actually seem benefited by surgical drainage of the bile ducts. The chief problem is how long delay is justifiable when obstructive jaundice is present. The risk of postponing surgical intervention is much greater in older patients, especially those with complete obstruction or those who have received no transfusions, plasma or parenteral medication in recent months.

TOXIC HEPATITIS

Toxic hepatitis is most commonly seen after exposure to hepatotoxic agents, such as chlorinated hydrocarbons, arsenic and alcohol, which may produce disturbances of intracellular enzyme systems and metabolic derangements of the parenchymal cells as well as actual necrosis. Fatty and hyaline infiltrations, hydremic swelling, irregularities of the lobular arrangement, altered structure and staining reactions and prominent multinucleation may be demonstrable on biopsy. The liver is usually enlarged and firm. Jaundice is variable in intensity and the disturbances of metabolic function are unpredictable. In chronic carbon tetrachloride poisoning, for example, a relative lowering of serum cholesterol ester

may be the only significant abnormal sign. The cephalin flocculation reaction may be negative or only weakly positive in these cases, unless injury is severe and active breakdown of tissue of the liver is also taking place. A negative reaction cannot, therefore, be used to exclude chronic hepatic damage in persons habitually exposed to potentially injurious substances. The serum alkaline phosphatase level usually is not elevated in toxic hepatic states, and this observation is often of great importance in ruling out conditions requiring surgical management.

NEOPLASMS OF THE LIVER

Neoplastic involvement of the liver may be metastatic or may arise primarily from the hepatic or biliary tissues. The liver is usually enlarged, irregular and firm. Jaundice and ascites may or may not be present. The differentiation from cirrhosis, hepatic abscess, granulomas and intrahepatic thrombosis (Chiari's syndrome) is often difficult, since the laboratory findings and clinical features may be quite similar in all these diseases. In about one third of all cases of malignant tumors of the liver, the serum alkaline phosphatase is elevated. The cephalin flocculation reaction is usually negative, unless active cirrhosis is present or widespread disturbance of blood supply leads to anoxia and necrosis of hepatic tissue. It is doubtful that reactions to any combination of laboratory tests is ever sufficiently reliable to establish or rule out the diagnosis of malignant growth. Here again, if the situation is at all questionable, surgical exploration is indicated for proper evaluation and management.

Much progress has been made during the past decade in the diagnosis of jaundice by laboratory aid. It is important to realize that limitations to the present methods still exist. In order to avail oneself of all the advantages of modern therapy, it is essential that the nature and extent of the disease are determined as accurately as possible in every instance. Prolonged rest in bed and costly medication should not be directed uncritically or by guess work. At present many laparotomies can be avoided, but one must still rely heavily on the surgeon to elucidate complex derangements of the liver. Perhaps by more careful correlation of the clinical features with improved understanding of hepatic physiology, fewer diagnostic and therapeutic atrocities will mar case records.

CONCLUSIONS

The transport of bilirubin from the blood to the biliary system is a specific function of the parenchymal cells of the liver; however, the mechanisms regulating the excretion of bile are but poorly understood.

Jaundice may be caused by any disorder leading to destruction or functional derangement of the hepatic unit or to obstruction of the biliary passages, either within or without the liver.

Uncomplicated obstructive jaundice usually can be distinguished from hepatocellular jaundice by the employment of a few simple tests, such as determination of the serum alkaline phosphatase level to evaluate the obstructive factor and the cephalin flocculation and thymol turbidity tests to detect the presence or absence of inflammatory or necrotizing processes within the liver.

Primary cholangiolitis, chronic hepatic intoxication and neoplastic and granulomatous infiltrations of the liver, for reasons stated in the text, often cannot be identified with certainty by the reactions to any combination of laboratory tests.

Biopsy of the liver is justifiable when the diagnosis is in doubt, but surgical exploration, rather than the trocar technic, is indicated when the picture is that of obstructive jaundice.

TIME ACTION OF GLOBIN INSULIN COMPARED WITH THAT OF PROTAMINE INSULIN MODIFICATIONS

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IN THE routine daily treatment of diabetes mellitus with insulin the depot insulins have become almost universally accepted as standard because of their ability to maintain smoother control of diabetes with fewer hypodermic injections. They have almost completely replaced the ordinary solutions of the hormone, "regular" or "plain" insulin and "crystalline" insulin, in the day by day maintenance therapy of diabetes. The ordinary soluble preparations of the hormone have such an intense and brief action that they are unsuitable for maintenance therapy by themselves. Their use is confined chiefly to the treatment of emergencies in diabetes in which prompt action is required, to augmentation of the slow action of depot insulins when this is desirable, to treatment of occasional patients who are allergic or unresponsive to the depot insulins and to induction of shock in psychotherapy.

How do the various depot insulins compare with one another and what are the indications for each in management of diabetes? These details are not so well known, even after almost fifteen years of experience with one of them.[1] For fully ten years it has become increasingly apparent that the sustained, weak action of the oldest of the depot insulins, protamine zinc insulin, is too slow and uncertain for best control of severe forms of diabetes mellitus. Its great advantage of prolonged effect has also been its chief fault, because its action after injec-

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1. Hagedorn, H. C.; Jensen, N.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177-180 (Jan. 18) 1936. Joslin, E. P.; Root, H. F.; Marble, A.; White, P.; Joslin, A. P., and Lynch, G. W.: Protamine Insulin, New England J. Med. **214**:1079-1085 (May 28) 1936. Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, Am. J. M. Sc. **192**:589-600 (Nov.) 1936.

tion in the morning has been so weak that patients with severe diabetes tend to excrete large amounts of sugar after eating ordinary meals.[2] If the amount given is increased in an effort to reduce or clear this postcibal glycosuria, severe insulin shock is likely to occur during sleep and exercise. In control of milder forms of diabetes it has been eminently satisfactory because details of insulin timing then are not important and its timing faults are not apparent.

A third type of insulin, therefore, has been developed for use in severe diabetes. It is commonly known as "intermediate" insulin because its effects are about midway, on the average, in speed, intensity and duration between those characteristic of ordinary insulin in solution at one extreme and those typical of protamine zinc insulin at the other. Intermediate insulin preparations have come into widespread use in severe diabetes because of their greater efficiency and convenience. Results of fully ten years of careful testing and clinical experience are now available with some of them. Their value has been established clinically to the extent that most diabetic patients now using them would not revert to older, less efficient forms of insulin even if advised to do so. Confirmation of their value has appeared in the literature from many sources, both here and abroad. Any one of them probably could replace protamine zinc insulin without any important disadvantages.

REVIEW OF INTERMEDIATE INSULIN PRODUCTS

In this country three specific preparations with intermediate action have been studied and used extensively. It is the purpose of this report to show how they compare with each other by means of time action curves[3]; the results obtained have been amply confirmed by clinical application.

1. *Globin Insulin with Zinc.*—Introduced by Reiner, Searle and Lang in 1939,[4] this preparation, commercially available from two manufac-

2. Lawrence, R. D., and Archer, N.: Some Experiments with Protamine Insulinate, Brit. M. J. **1**:747-749 (April 11) 1936. Joslin, E. P.: Difficulties in the Use of Protamine Zinc Insulin, J. A. M. A. **110**:90-91 (Jan. 8) 1938. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, ibid. **110**:92-96 (Jan. 8) 1936.

3. Colwell, A. R.; Izzo, J. L., and Stryker, W. A.: Intermediate Action of Mixtures of Soluble Insulin and Protamine Zinc Insulin, Arch. Int. Med. **69**:931-951 (June) 1942.

4. Reiner, L.; Searle, D. S., and Lang, E. H.: Insulin Preparations with Prolonged Activity: Globin Insulin, Proc. Soc. Exper. Biol. & Med. **40**:171 (Feb.) 1939; On the Hypoglycemic Activity of Globin Insulin, J. Pharmacol. & Exper. Therap. **67**:330-340 (Nov.) 1939.

turers in this country, has been studied extensively [5] and compared clinically with protamine zinc insulin.[6] It is an insulin compound with beef globin and zinc which is in slightly acid solution rather than in suspension (as the other intermediate insulins are). We have previously reported action curves for globin insulin and some of its modifications,[7] as well as preliminary comparisons of it with commonly used protamine insulin modifications.[8] It probably depends for its intermediate action on a combination of rapid and slow absorption due to the fact that it is partially precipitated on neutralization by tissue fluids after subcutaneous injection.

2. *Insulin and Protamine Zinc Insulin Mixtures.*—Ulrich was the first to demonstrate the results of mixing ordinary insulin with commercially available preparations of protamine zinc insulin.[9] He reported that it is necessary to use more insulin than protamine zinc insulin in such mixtures to alter the action of protamine zinc insulin appreciably. Colwell and his associates then reported on a series of investigations of the

5. Bauman, L.: Clinical Experience with Globin Insulin, Am. J. M. Sc. **198**:475-481 (Oct.) 1939. Marks, H. E.: A New Globin Insulin, M. Clin. North America **24**:649-670 (May) 1940. Martin, H. E.; Simonsen, D. G., and Homan, N. H.: Time Activity Curves of Globin Insulin with Clinical Applications, Am. J. M. Sc. **208**:321-332 (Sept.) 1944. Mosenthal, H. O.: Globin Insulin with Zinc in the Treatment of Diabetes Mellitus, J. A. M. A. **125**:483-488 (June 17) 1944. Jackson, R. L., and McIntosh, C. B.: Globin Insulin in the Treatment of Children with Diabetes Mellitus, Proc. Am. Diabetes A. **5**:99-116, 1945. Sheppe, W. M., and Sheppe, W. M., Jr.: The Evaluation of Globin Insulin in the Treatment of Diabetes Mellitus, West Virginia M. J. **45**:79-83 (April) 1949.

6. Duncan, G. G., and Barnes, C. E.: The Action of Globin Insulin Compared with That of Crystalline, Unmodified, and Protamine Zinc Insulin, Am. J. M. Sc. **202**:553-563 (Oct.) 1941. Bailey, C. C., and Marble, A.: Histone Zinc Insulin, Globin (Zinc) Insulin and Clear Protamine Zinc Insulin, J. A. M. A. **118**:683-690 (Feb. 28) 1942. Protas, M.: Comparative Study of Action of Globin Insulin with Other Forms of Insulin, M. Ann. District of Columbia **13**:254-257 (July) 1944. Sindoni, A.: Present Day Conception of Protamine Zinc Insulin and Globin Insulin with Zinc, Delaware State M. J. **18**:21-32 (Feb.) 1946. Roberts, J. T., and Yater, W. M.: Comparison of the Clinical Use of Protamine Zinc Insulin and Globin Insulin in Equal Doses, Ann. Int. Med. **26**:41-66 (Jan.) 1947. Rabinowitch, I. M.; Fowler, A. F.; Beasley, E. H.; Gordon, A. L., and Mountford, M.: Globin Insulin, Canad. M. A. J. **56**:595-604 (June) 1947. Wauchope, G. M.: Globin Insulin: A Clinical Study, Brit. M. J. **2**:191-194 (July 24) 1948.

7. Rohr, J. H., and Colwell, A. R.: Comparative Time Action of Globin Insulins, Arch. Int. Med. **82**:54-62 (July) 1948.

8. Rohr, J. H., and Colwell, A. R.: Comparison of Intermediate Insulins, Proc. Am. Diabetes A. **8**:3-11, 1948.

9. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, Ann. Int. Med. **14**:1166-1179 (Jan.) 1941.

standard insulins and their mixtures,[10] which indicated that mixtures containing at least twice as much insulin as protamine zinc insulin were most suitable for use in severe diabetes. Studies of mixtures of protamine zinc insulin and insulin have been reported on by many others, notably Peck,[11] Sprague,[12] Palmer [13] and Izzo.[14] The mixtures have come into common use as convenient and effective substitutes for protamine zinc insulin alone or together with regular insulin by separate injection. The most commonly used of these mixtures is undoubtedly the "2:1 mixture," made extemporaneously by mixing thoroughly (in the syringe or preferably an empty ampul) twice as much regular or crystalline insulin as protamine zinc insulin, both in the 80 unit concentration. This mixture has been used for comparison with the other well known intermediate preparations in the present report.

3. *Crystalline Protamine Insulin* (NPC-50 or NPH-50).—In 1946 a recrystallized form of protamine insulin was prepared in Hagedorn's laboratory which contained about 40 per cent as much protamine as the commercially available preparation,[15] slightly more than the commonly

10. Colwell and associates.[8] Colwell, A. R., and Izzo, J. L.: Protamine Zinc Insulin Modified for Accelerated Action, J. A. M. A. **122**:1231-1236 (Aug. 28) 1943. Colwell, A. R.: Nature and Time Action of Modifications of Protamine Zinc Insulin, Arch. Int. Med. **74**:331-345 (Nov.) 1944; Protamine Insulin Mixtures in the Treatment of Diabetes Mellitus, New York State J. Med. **47**:1103-1110 (May 15) 1947; Effective Insulin Timing in Diabetes Mellitus, M. Clin. North America **31**:327-341 (March) 1947; Problems in Treatment of Diabetes Mellitus, Pennsylvania M. J. **52**:1638-1643 (Dec.) 1949; Diabetes Mellitus: Treatment with Intermediate Insulins, J. Missouri M. A. **113**:117 (Feb.) 1950.

11. (*a*) Peck, F. B.: Action of Insulins, Proc. Am. Diabetes A. **2**:69-83, 1942; (*b*) Treatment of Uncomplicated Diabetes with Mixtures of Insulin and Protamine Zinc Insulin, J. Indiana M. A. **36**:340-348 (July) 1943; (*c*) Approximate Insulin Content of Extemporaneous Mixtures of Insulin and Protamine Zinc Insulin, Ann. Int. Med. **18**:177-181 (Feb.) 1943. (*d*) Peck, F. B., and Schechter, J. S.: Newer Insulin Mixtures: Follow-Up Study, Proc. Am. Diabetes A. **4**:57-86, 1944. (*e*) Peck, F. B.: Insulin Mixtures and Modifications, ibid. **6**:275-300, 1946; (*f*) Insulin Mixtures and Modifications, M. Clin. North America **31**:343-357 (March) 1947.

12. Sprague, R. G.: The Use of Various Kinds of Insulin, M. Clin. North America **30**:933-944 (July) 1946. Sprague, R. G., and Underdahl, L. O.: The Use of Insulin Mixtures, Minnesota Med. **30**:153-156 (Feb.) 1947. Sprague, R. G.: The Use of Mixtures of Protamine Zinc and Regular Insulin, Ann. Int. Med. **30**:628-636 (Oct.) 1949.

13. Palmer, L. J.: Insulin in the Treatment of Diabetes Mellitus, J. A. M. A. **132**:502-507 (Nov. 2) 1946. Palmer, L. J., and Crampton, J. H.: Experience with Insulin Mixtures, Am. J. Med. **3**:167-170 (Aug.) 1947.

14. Izzo, J. L.: Studies on Modified Insulins, Proc. Am. Diabetes A. **9**: 227-243, 1949.

15. Krayenbühl, C., and Rosenberg, T.: Crystalline Protamine Insulin, Reports Steno Memorial Hosp. **1**:60-73, 1946. Hagdorn, H. C., in discussion on Peck.11e

used "2:1 mixture." Peck demonstrated its time action to be of a clearly intermediate character,[15e] and for the last two or three years commercially produced preparations distributed for clinical trial have been tested by various observers.[16] It is a neutral suspension of uniform crystals, stable enough for clinical use and fairly constant in its protamine content, hence with certain advantages over mixtures of protamine zinc insulin and insulin.

A fourth preparation serving the purpose of the intermediate insulins very well has been studied extensively by MacBryde and his associates.[17] It has been called NP-50 and "modified protamine zinc insulin." This product should not be confused with NPC-50 or NPH-50. It was made by an insulin manufacturer to duplicate the action of ordinary and protamine zinc insulin given by separate injection. Prepared in such a way that about one-fourth of its insulin was in solution and three-fourths in suspension as protamine insulin, it gave a combined rapid and slow effect; thus its action compared favorably with that of other intermediate preparations in clinical trials. Because its action was presumably diphasic and therefore, not strictly intermediate in character and because it was subsequently shown not to be stable in its soluble insulin component, the preparation was not included in the present study, in spite of its promising features described by MacBryde and others.

In the present study, the three intermediate insulins were compared with each other by means of time action curves of the blood and urinary sugar in human diabetes mellitus after hypodermic injection of single large doses.[18] This method has been found most dependable for comparative testing of insulin timing and intensity of action and as a guide for therapeutic indications of various preparations.[19] These studies,

16. Gabrielle, A. J., and Marble, A.: Clinical Experience with a New Modified Protamine Insulin (NPH-50), Am. J. Digest. Dis. **16**:197-206 (June) 1949. White, P.: Modified Protamine Insulin (NPH-50), J. A. M. A. **141**:312-314 (Oct. 1) 1949. Dolger, H.: Prepared Insulin Mixtures in the Treatment of the Severe Diabetic Patient, Proc. Am. Diabetes A. **9**:203-211, 1949. Marble, A., and Gabrielle, A. J.: Studies with a New Modified Protamine Insulin (NPH-50-Lilly), ibid. **9**:215-223, 1949.

17. MacBryde, C. M., and Roberts, H. K.: Modified Protamine Zinc Insulin: An Improvement on Standard Protamine Zinc Insulin, J. A. M. A. **122**:1225-1231 (Aug. 28) 1943; A New Modified Protamine Zinc Insulin: Comparison with Histone Zinc Insulin, Clear, and Standard Protamine Zinc Insulins, J. Clin. Investigation **22**:791-797 (Nov.) 1943. MacBryde, C. M., and Reiss, R. S.: Modified Protamine Zinc Insulin: Comparison with Globin Zinc Insulin and Insulin Mixtures, J. Clin. Endocrinol. **4**:469-479 (Oct.) 1944.

18. The globin insulin used in these experiments was supplied by Burroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y. The mixture of insulin and protamine zinc insulin and the crystalline protamine insulin were supplied by Eli Lilly & Company, Indianapolis 6.

19. Colwell and others.[3] Rohr and Colwell.[7]

as well as clinical experience, demonstrate that there is little difference in action among the three preparations and that a choice for therapeutic use must be based on other considerations than their timing characteristics.

METHODS OF STUDY

The methods of study have been described in detail in earlier reports[20] and will be summarized briefly. Two patients with diabetes of moderate severity were fed meals of approximately uniform value every four hours, night and day, week after week in the hospital with little exercise. Urinary and blood sugar levels were determined every four to twelve hours until they became relatively constant. Tendencies for afternoon sugar levels to drop below night levels were corrected by giving larger amounts of food during the day than at night. No insulin was used until single doses were tested.

After fair constancy of blood and urinary sugar at high levels was accomplished, single 60 unit doses of the insulins to be tested were injected subcutaneously and their effects determined by observing the reduction in the sugar levels. No further insulin was given until these effects were exhausted and former levels of blood and urinary sugar reestablished.

Because of variations in individual curves obtained in this fashion, repeated determinations were made with each insulin preparation and the results in each patient were averaged at each interval after injection. In this manner fairly smooth action curves characteristic of each insulin product were obtained for comparison. (This is the method in common use for insulin assay with groups of animals and was, therefore, considered acceptable.)

RESULTS

Figures 1 and 2 show the average values for blood and urinary sugar obtained in this fashion for the 2 patients. In one patient (fig. 1, patient N) the curves for the three intermediate insulins are compared with each other and with those for plain and protamine zinc insulins. In the other (fig. 2, patient H) curves for only two of the three intermediate insulins are compared with each other and with curves for the standard insulins. Sixty unit doses were used in all experiments. The curves represent averages of one to fourteen individual experiments, as indicated.

For orientation, the familiar curves for the rapid, intense and brief action of regular insulin (figs. 1 *A* and 2 *A*) and the slow, weak and sustained action of protamine zinc insulin (figs. 1 *E* and 2 *D*) are included. They demonstrate that the methods of investigation and the patients used are capable of reflecting differences in intensity and duration of action of the insulins studied. The observations emphasize the intermediate character of the three other preparations (figs. 1 *B* to *D* and 2 *B* and *C*). The control levels and responses to standard insulins suggest that the first patient (N) had diabetes of less severity and was less sensitive to insulin than the second (H).

20. Colwell and others.[10] Rohr and Colwell.[7]

In patient N (fig. 1) the differences in action of globin insulin, a 2:1 mixture and crystalline protamine insulin (NPC 50) appeared to be within the limits of error of the method of study. Average curves for

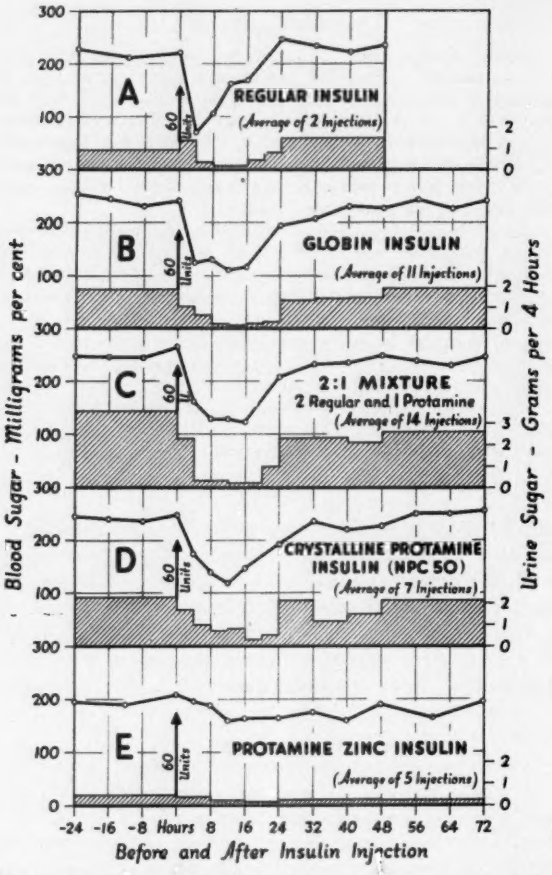

Fig. 1. (patient N).—Average blood and urinary sugar curves before and after subcutaneous injection of 60 unit doses of (*A*) regular insulin, (*B*) globin zinc insulin, (*C*) mixture of two parts regular with one part protamine zinc insulin, (*D*) crystalline protamine insulin (NPC-50) and (*E*) standard protamine zinc insulin. The curves for the three intermediate insulins are similar to each other and quite different from those for the two standard preparations.

eleven injections of the first (fig. 1 *B*), fourteen injections of the second (fig. 1 *C*) and seven injections of the third (fig. 1 *D*) show all to have

prompt and fairly strong effects at four hours, peak effects from eight to sixteen hours, waning effects at twenty-four hours and weak action into the second day after injection. The differences among them were

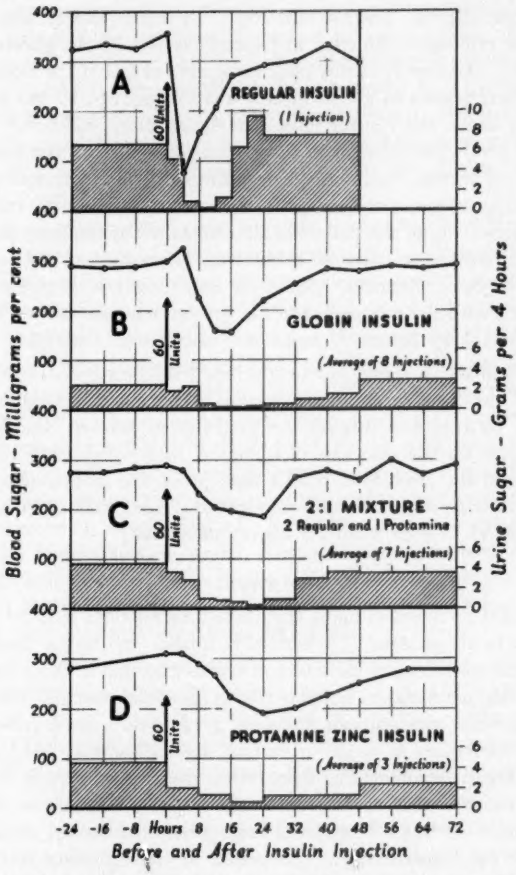

Fig. 2 (patient H).—Average blood and urinary sugar curves before and after subcutaneous injection of 60 unit doses of (*A*) regular insulin, (*B*) globin zinc insulin, (*C*) mixture of two parts regular with one part protamine zinc insulin, and (*D*) standard protamine zinc insulin. Minor differences between the curves for the two intermediate insulins probably are not of clinical importance.

insignificant, in this patient at least, when compared with the differences between any of them and regular or protamine zinc insulin.

In patient H (fig. 2) curves for globin insulin and a 2:1 mixture were compared. The two preparations were intermediate in action between regular and protamine zinc insulins, as in patient N. In addition, there appeared to be minor differences in their effect, seen best in the blood sugar curves. The mixture (fig. 2 *C*) caused slower, less intense and more prolonged reduction in hyperglycemia than the globin insulin (fig. 2 *B*). However, in this patient the rate of fall of the blood sugar after administration of globin insulin was exaggerated by the irregular elevation above the control level four hours after injection. Within limits of error, the behavior of the glycosuria was about the same after injection of each of the intermediate insulins. The differences in blood sugar response are, therefore, probably more apparent than real. The greater sensitivity of this patient to all insulins tested may have permitted minor differences to manifest themselves, in contrast to the results in patient N, but the smaller number of tests (eight with globin insulin and seven with the mixture) and the greater irregularities of response to all insulins by patient H make this assumption doubtful.

In summary, it seems fair to conclude that the responses to 60 unit doses of the three intermediate insulins were approximately the same in these patients and that all the preparations showed decidedly less prompt and intense reactions than regular insulin but more rapid and intense and less prolonged results than protamine zinc insulin. They exerted their strongest effects from eight to sixteen hours after injection. These effects were exhausted gradually thereafter.

COMMENT

There is no intent to imply that these time relations hold for all sizes of doses in all patients. Undoubtedly, smaller and larger doses given to patients with diabetes more or less severe than that in these 2 subjects would bring out variables not apparent in these experiments. Differences in extracellular subcutaneous fluids and proteolytic enzyme systems may lead to differences in action in various diabetic persons which are not evident here. Accumulating depot effects from repeated daily injections in routine treatment of diabetes might reveal differences in behavior which could not be predicted from single dose experiments, as suggested by Peck and Schechter.[11d] The period of waning effect is the most difficult to measure accurately; yet it is the most important period in overlapping of repeated daily injections. That any or all of these factors may be important is evident in ordinary clinical experience with depot insulins.

Even so, the fact that large doses of these insulins in patients with diabetes of moderate severity act so much alike and so differently from

the standard insulins with which they were compared indicates that they all occupy a relatively intermediate position and are not radically different from one another.

The clinical application of this knowledge is readily apparent. An insulin used once daily before breakfast should fit the normal eating and sleeping habits of the individual patient as well as possible. It should span a twenty-four hour period; it should not cause reactions at any time of day and its effects should not wane so rapidly as to permit heavy glycosuria in the hours of overlapping (after breakfast, with daily morning injections). Because most severely diabetic patients require 40 to 80 units daily for best control, these specifications should hold for single doses of about 60 units.

The great usefulness of protamine zinc insulin has been due to the fact that it meets some of these requirements. In moderate diabetes, in which details of insulin timing are unimportant, reactions and heavy glycosuria are unlikely to occur, large doses are usually not required and stability of control is easy to maintain, it serves its purpose effectively.

In severe forms of diabetes its faults can often be eliminated by the use of one of the intermediate preparations. The tendency for the patient to excrete large amounts of sugar after meals and to have unpredictable insulin shock during the night demands an insulin with more effective timing. In larger doses this should consist of action more intense in the first twelve hours after injection than in the next twelve hours, without sacrificing overlapping of effect from injections given every twenty-four hours. Globin insulin, mixtures containing about twice as much regular as protamine zinc insulin and crystalline protamine insulin all exhibit this desirable type of action and are almost indistinguishable from one another in their effects, on the average.

For any given patient with severe diabetes mellitus the most suitable insulin preparation can be determined only by trial and comparison, because the size of the dose required and the severity of the diabetes lead to differences in response which are more important than demonstrable differences in action among the three intermediate preparations.

If one of the protamine insulin modifications is selected for commercial use, it should be easily modifiable by the patient. Increased intensity by addition of small amounts of insulin should be obtained easily when desirable. Added insulin should not affect the stability of the supplement or that of the original material. This type of alteration has been complicated with protamine zinc insulin as now manufactured. Previous studies indicated that it is difficult with globin insulin [7] and easy with protamine insulin mixtures.[10] Evidence concerning alteration of crystalline protamine insulin (NPC-50 or NPH-50) in this manner

is not yet available, but clinical experience indicates that stability is not affected and that the action of small amounts of added insulin is reflected by increased intensity as with the mixtures.

CONCLUSIONS

Globin insulin with zinc, crystalline protamine insulin (NPC-50 or NPH-50) and a mixture containing twice as much regular as protamine zinc insulin are all intermediate in rapidity, intensity and duration of action between ordinary insulin in solution and standard protamine zinc insulin. Differences in action among these three intermediate insulins are less important than differences in insulin requirement and response of various patients with diabetes mellitus. All three are superior to ordinary insulin and protamine zinc insulin in the routine treatment of patients with severe diabetes by injection once daily before breakfast.

Severe diabetes should be managed with the use of one of the intermediate insulins. The preparation which most closely fits the eating and fasting requirements of the individual patient in the smallest dosage should be determined in each case by trial.

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EFFECT OF FEEDING EGG YOLK AND CHOLESTEROL ON SERUM CHOLESTEROL LEVELS

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THE ROLE of exogenous cholesterol as a factor in the development of arteriosclerosis has received much attention and attempts to raise serum cholesterol levels in human beings have been made.[1] In general, it appears difficult to alter substantially serum cholesterol levels in normal human beings by feeding cholesterol or cholesterol-containing substances. Evidence concerning the reasons for this difficulty is accumulating. Endogenous sources of cholesterol appear to be of great importance.[2] One report suggested that cholesterol fed in the diet tends to depress synthesis in the body.[3]

Although the number of patients studied by us is small and the relation of plasma cholesterol levels to the development of arterial disease in man is not clear, it was thought worth while to report the results of the present study for two reasons: first, because of the duration of the experimental feeding periods and, second, because the results show clearly how difficult it is to alter plasma cholesterol levels by diet.

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1. (*a*) Duff, L. G.: Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis, Arch. Path. **20**:81 (July) 1935; 269 (Aug.) 1935. (*b*) Turner, K. B., and Steiner, A.: A Long Term Study of the Variation of Serum Cholesterol in Man, J. Clin. Investigation **18**:45 (Jan.) 1939. (*c*) Steiner, A., and Domanski, B.: Dietary Hypercholesterolemia, Am. J. M. Sc. **201**:820 (June) 1941.

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METHOD AND MATERIAL FOR FIRST THREE EXPERIMENTS

A number of patients of an age at which at least a small degree of arteriosclerosis might be presumed to be present were selected for study. Most of these

TABLE 1.—*Cholesterol Levels Before, During and After Feeding 150 Gm. of Egg Yolk Powder to Six Subjects*

Patient	Age, Yr.	Sex	Diagnosis	Control Cholesterol Level, Mg./100 Cc. Average	Control Cholesterol Level, Mg./100 Cc. Range	Average Cholesterol Level During Feeding of Egg Yolk Powder, Mg./100 Cc.	Average Increase, Mg./100 Cc.	Average Cholesterol Level 3 Wk. After Feeding Egg Yolk Powder, Mg./100 Cc.
H. H.	56	M	Rheumatoid arthritis and generalized arteriosclerosis	201	187 to 213	238	37	204
A. K.*	54	M	Rheumatoid arthritis, rheumatic heart disease and amyloid disease	244	237 to 280	271	27	263
J. L.*	61	M	Arteriosclerotic heart disease	198	195 to 203	259	61	246
C. S.	58	M	Arteriosclerotic heart disease	201	195 to 213	229	28	216
E. Z.*	60	M	Arteriosclerotic heart disease	176	163 to 190	207	31	189
A. S.*	57	M	Hypertensive vascular disease, arteriosclerotic heart disease and coarctation of the aorta	166	163 to 180	203	37	198

* As noted in the text, these patients were used in more than one experiment.

TABLE 2.—*Cholesterol Levels Before, During and After Feeding 150 Gm. of Egg Yolk Powder to Ten Subjects*

Patient	Age, Yr.	Sex	Diagnosis	Control Cholesterol Level, Mg./100 Cc. Average	Control Cholesterol Level, Mg./100 Cc. Range	Average Cholesterol Level During Feeding of Egg Yolk Powder, Mg./100 Cc.	Average Increase, Mg./100 Cc.	Average Cholesterol Level 4 Wk. After Feeding Egg Yolk Powder, Mg./100 Cc.
N. B.	52	F	Arteriosclerotic heart disease; syphilitic aneurysm of aorta	187	186 to 192	207	20	189
A. K.*	54	M	Rheumatoid arthritis, rheumatic heart disease and amyloid disease	282	237 to 284	298	16	278
J. L.*	61	M	Arteriosclerotic heart disease	206	195 to 210	249	13	214
J. S.	64	M	Arteriosclerotic heart disease	240	229 to 250	261	21	264
E. Z.*	60	M	Arteriosclerotic heart disease	178	160 to 190	206	28	178
A. S.*	57	M	Hypertensive vascular disease, arteriosclerotic heart disease and coarctation of the aorta	187	163 to 194	225	38	183
E. M.	55	M	Arteriosclerotic heart disease	221	225 to 265	292	71	258
I. W.	66	M	Boeck's sarcoid	173	169 to 184	224	51	173
S. P.	61	M	Generalized arteriosclerosis	221	204 to 244	292	71	238
E. W.	66	M	Latent syphilis; rheumatic heart disease	278	277 to 313	279	10	290

* As noted in the text, these patients were used in more than one experiment.

exhibited a considerable degree of arteriosclerosis but were otherwise free of obvious disease. A few of the group were included because clinical manifestations of arteriosclerosis were entirely lacking (tables 1, 2 and 3). The cholesterol level of each patient was determined weekly prior to, during and after each feeding experiment. All consumed the regular hospital diet containing, on the average, 70 Gm. of

fat daily. The modified method of Schoenheimer and Sperry [4] was used for the cholesterol determinations.

In the first experiment (table 1) 6 patients were fed 150 Gm. of egg yolk powder containing 2.5 per cent cholesterol and 15.2 per cent lecithin on analysis. The powder was emulsified in 400 cc. of milk and fed twice daily for forty-eight days. In a second experiment (table 2) 10 patients, 4 of whom (A. K., J. L., E. Z. and A. S.) were also subjects of the first experiment, were fed a similar diet. The control period was forty-eight days and the feeding period forty-two. In a third experiment (table 3) 8 patients were fed 100 instead of 150 Gm. of egg yolk powder daily. One patient, A. S., had served as a subject in the two previous experiments. After the period of feeding egg yolk powder, cholesterol levels were followed for three weeks in the first experiment and for four weeks in the second and third experiments. These studies were completed in 1942. In retrospect, longer postfeeding periods of observation would have been desirable, since some

TABLE 3.—*Cholesterol Levels Before, During and After Feeding 100 Gm. of Egg Yolk Powder to Eight Subjects*

Patient	Age, Yr.	Sex	Diagnosis	Control Cholesterol Level, Mg./100 Cc.		Average Cholesterol Level During Feeding of Egg Yolk Powder, Mg./100 Cc.	Average Increase, Mg./100 Cc.	Average Cholesterol Level 4 Wk. After Feeding Egg Yolk Powder, Mg./100 Cc.
				Average	Range			
V. G.	69	M	Generalized arteriosclerosis	324	312 to 352	341	17	314
A. K.	59	M	Arteriosclerotic heart disease	309	290 to 338	327	18	294
H. Y.	66	F	Generalized arteriosclerosis	201	187 to 218	213	12	197
E. W.	63	M	Generalized arteriosclerosis	231	208 to 253	264	33	263
A. J.	65	F	Generalized arteriosclerosis	178	166 to 193	209	33	190
A. S.*	57	M	Hypertensive vascular disease, arteriosclerotic heart disease and coarctation of the aorta	187	164 to 192	215	28	213
M. W.	64	F	Generalized arteriosclerosis	230	215 to 257	264	34	225
J. W.	46	M	Tabes dorsalis	158	150 to 169	171	13	162

* As noted in the text, this patient was used in more than one expediment.

of the serum cholesterol values failed to return to the prefeeding levels even after four weeks.

RESULTS OF FIRST THREE EXPERIMENTS

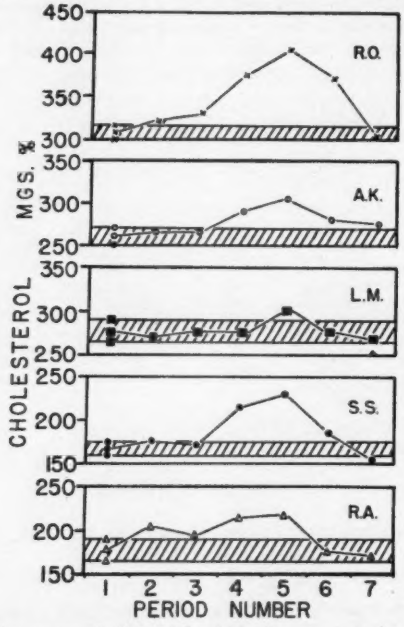
The subjects exhibited the usual range of fasting serum cholesterol levels encountered among apparently healthy persons (tables 1, 2 and 3). Most patients, some on more than one occasion, showed an increase in serum cholesterol values after the feeding of egg yolk powder. It appears, therefore, that egg yolk powder contains a substance capable of altering the absorption or disposition of cholesterol. Steiner and Domanski [1c] at one time held the opinion that the phospholipid lecithin in egg yolk was perhaps responsible for the increase in serum cholesterol when egg yolk powder was fed to their subjects.

4. Schoenheimer, R., and Sperry, W. M.: Micromethod for Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745 (Sept.) 1934.

METHOD AND MATERIAL FOR FOURTH EXPERIMENT

Because cholesterol is the constituent of egg yolk powder in which interest centers, a fourth experiment was designed in 1947 to compare the effect on the serum cholesterol level of feeding pure cholesterol in various forms with that of feeding egg yolk powder. The experiment was conducted in the following manner.

Five men, who were not suffering from active disease processes but who were in the same age group (45 to 65 years) as the previous subjects and, therefore, presumably had some degree of arteriosclerosis, were selected. During an initial control period of fifty-nine days the patients consumed the usual hospital



Graph showing serum cholesterol levels in 5 persons during various dietary regimens. Cross-hatched areas indicate the degree of variation in the control level of serum cholesterol for each subject. The description of the dietary supplements employed in each period for which the average serum cholesterol is charted follows: First period, no dietary supplement (control period); second period, 30 Gm. of crystalline cholesterol for twenty-nine days followed by sixty-six day rest period; third period, 200 cc. of 40 per cent cream daily for twenty days, followed immediately by (fourth period) 200 cc. of 40 per cent cream plus 30 Gm. of crystalline cholesterol daily for sixty-six days, followed immediately by (fifth period) 150 Gm. of egg yolk powder daily for fifty days, followed by twenty-six day rest period; sixth period, 15 Gm. of amorphous cholesterol daily for thirty days, increased to 30 Gm. daily for an additional thirty-three days (1 patient [L. M.] declined this feeding) and seventh period, no dietary supplement (control period).

diet which contained, on the average, 70 Gm. of fat daily, supplemented by 400 cc. of milk daily. Blood cholesterol levels were obtained weekly at the beginning, during and after feeding experiments.

First, 30 Gm. of crystalline cholesterol, suspended in the milk, was fed daily for twenty-nine days in addition to the regular diet. Second, after a rest period of sixty-six days, 200 cc. of 40 per cent cream was fed in addition to the regular diet for twenty days. Third, 30 Gm. of crystalline cholesterol was added to the cream for an additional sixty-six days. Fourth, without further control period, the cream and cholesterol feedings were discontinued and 150 Gm. of egg yolk powder divided into two doses and suspended in the usual 400 cc. of milk was fed for fifty days. Finally, after a control period of twenty-six days, 15 Gm. of amorphous cholesterol was fed in the usual amounts of milk daily for thirty days and then increased to 15 Gm. twice daily for an additional thirty-three days. One subject (L. M.) declined the feedings in this final period.

RESULTS OF FOURTH EXPERIMENT

This study, designed to test the effect of feeding cholesterol in various forms (figure), shows clearly that higher cholesterol levels follow the feeding of egg yolk powder than follow the feeding of much larger amounts of cholesterol in pure form. When cream and cholesterol were fed together, the rise was greater than with cholesterol or cream alone. It should be emphasized again that the amount of cholesterol in the egg yolk (approximately 3.5 Gm.) was much less than the amount of pure cholesterol used (15 to 30 Gm.).

COMMENT

Corwin's [5] observations on hypercholesteremia in dogs as a result of feeding lecithin derived from adrenal gland led Steiner and Domanski [1c] to use egg yolk powder as the source of lecithin in their experiments. Our initial experiments were undertaken to confirm this effect of egg yolk powder, and it is clear that the patients did exhibit increases in serum cholesterol values (tables 1, 2 and 3). The more recent study compared the effect of egg yolk powder with that of various forms of pure cholesterol. The results again confirmed the fact that feeding egg yolk powder was followed by rises in serum cholesterol levels and that these rises were greater than when pure cholesterol with or without added fat was administered (figure).

Since the subjects ingested only 3.75 Gm. of cholesterol in the egg yolk powder in twenty-four hours, the cholesterol content of the egg yolk powder appeared relatively unimportant. This study was begun with the notion that the effective substance might be lecithin. But Steiner and Domanski [6] have noted lowering of cholesterol content following the feeding of soy bean lecithin to human beings, and Delevett

5. Corwin, W. C.: Experimental Hypercholesteremia in Dogs, Arch. Path. **26**:456 (Aug.) 1938.

6. Steiner, A., and Domanski, B.: Effect of Feeding "Soya Lecithin" on Serum Cholesterol Level of Man, Proc. Soc. Exper. Biol. & Med. **55**:236 (April) 1944.

and Bruger [7] were unable to alter serum cholesterol levels by administration of soy bean lecithin to a group of patients, each of whom had persistently elevated serum cholesterol values. Our studies confirm the fact that there is, nonetheless, some substance in egg yolk powder which elevates serum cholesterol. The substance is probably neither cholesterol nor lecithin. Other constituents of egg yolk are being studied.

The elevations of blood cholesterol in these patients following the feeding of egg yolk powder were definite but certainly not great. It is difficult, moreover, either to elevate or to lower cholesterol levels by changing the intake of cholesterol. Dock [8] has suggested that the latter procedure might be of value. The fact that cholesterol is regularly formed in the body from acetate and acetone, as clearly demonstrated by Rittenberg, Bloch and their associates,[2] limits the importance of dietary intake in controlling serum levels. The practicability of lowering the serum level, and thus preventing deposition of cholesterol in atheromatous plaques, by withholding cholesterol from the diet seems, therefore, questionable.

Although the level of cholesterol is undoubtedly related to the development of atherosclerosis, other factors have recently been suggested as being of greater importance. For example, the ratio of phospholipids to cholesterol [9] and physicochemical changes in dispersion of blood lipids [10] both appear to be of considerable importance. These recent observations are in accord with the earlier ones of Landé and Sperry.[11] They were unable to show any relation between blood cholesterol content and the severity of atherosclerosis present at necropsy.

CONCLUSION

In three experiments in which 24 subjects were fed egg yolk powder in varying amounts in addition to their regular diet, the majority exhibited an increase in their serum cholesterol values. In a fourth experiment, 5 subjects were fed cholesterol in a variety of forms,

7. Delevett, A. F., and Bruger, F.: Plasma Lipids in Primary and in Secondary Hypercholesteremia, Arch. Int. Med. **81**:859 (June) 1948.

8. Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries, J. A. M. A. **131**:875 (July 13) 1946.

9. Davidson, J. D.; Abell, L. L., and Kendall, F. E.: Serum Lipids in Experimental Canine Arteriosclerosis, Am. Heart J. **38**:462 (Sept.) 1949.

10. Moreton, J. R.: Atherosclerosis and Alimentary Hyperlipemia, Science **106**:190 (Aug. 29) 1947. Gofman, J. W., and others: The Role of Lipids and Lipoproteins in Atherosclerosis, ibid. **111**:166 (Feb. 17) 1950.

11. Landé, K. E., and Sperry, W. M.: Human Atherosclerosis in Relation to Cholesterol Content of Blood Serum, Arch. Path. **22**:301 (Sept.) 1936.

including egg yolk powder. Egg yolk powder proved to be more effective than preparations of pure cholesterol in elevating the serum cholesterol values of most subjects.

It is concluded that there is a substance as yet unidentified in egg yolk which elevates the cholesterol level of human serums. The amount necessary to produce this result is well above that in the amount of egg yolk consumed in the ordinary diet.

Welfare Island (17).

INTRAVENTRICULAR BLOCK

Review of the Literature

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AND

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CHICAGO

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INTRODUCTION

THE CONCEPT of bundle branch block was introduced by Eppinger and Rothberger [1] in 1909 in Vienna, when, during the course of electrocardiographic studies of the effects of trauma to the myocardium induced by the injection of silver nitrate solution, they suspected that the appearance of broadened ventricular complexes meant damage to a main bundle branch. During the next few years, they studied this prob-

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From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital. The department is supported in part by the Michael Reese Research Foundation.

1. Eppinger, H., and Rothberger, C. J.: Zur Analyse des Elektrokardiogramms, Wien. klin. Wchnschr. **22**:1091, 1909.

lem experimentally in dogs.[2] Barker and Hirschfelder[3] in 1909 independently reported results they obtained by cutting the left main bundle branch of the canine heart. By this time the electrocardiogram had been introduced into the clinic, and Eppinger and Stoerck[4] were able to find 5 patients with intraventricular block in 1910. Four cases were reported by Mathewson[5] in 1912. Two years later Carter[6] discovered 22 instances in the electrocardiograms from various London hospitals and described the original criteria for the pattern of bundle branch block.

A wealth of literature has accumulated since the original concept was formulated. During the course of studies[7] on intraventricular block, it became necessary for us to review existing publications. It was apparent that some confusion was present and we felt that an organized synopsis would be valuable for those intersted in this topic. We have attempted to survey the literature on this subject published prior to 1950. It was impossible to include all papers dealing with intraventricular block; only the most pertinent literature is referred to in order to keep this review within reasonable limits. We have omitted consideration of the Wolff-Parkinson-White syndrome and the problem of intraventricular block complicated by myocardial infarction.

LEFT VERSUS RIGHT BUNDLE BRANCH BLOCK

The "orthodox" concept of the site of defective conduction rested on the early experiments performed in Vienna and was promulgated by Lewis[8] on the basis of his studies of the mammalian heart. In the presence of a pattern of intraventricular block, a main ventricular deflec-

2. (*a*) Eppinger, H., and Rothberger, W.: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med. **70**:1, 1910. (*b*) Rothberger, W., and Winterberg, H.: Experimentelle Beitraege zur Kenntnis der Reizleitungsstoerungen in den Kammern des Saeugetierherzens, Ztschr. f. d. ges. exper. Med. **5**:264, 1917.

3. Barker, L. F., and Hirschfelder, A. D.: The Effects of Cutting the Branch of the His Bundle Going to the Left Ventricle, Arch. Int. Med. **4**:193 (Sept.) 1909.

4. Eppinger, H., and Stoerck, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med. **71**:157, 1910.

5. Mathewson, G. D.: Lesions of the Branches of the Auriculo-Ventricular Bundle, Heart **4**:385, 1912.

6. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, Arch. Int. Med. **13**:803 (May) 1914.

7. Rosenman, R. H.; Pick, A., and Katz, L. N.: The Localization of Intraventricular Conduction Defects, to be published.

8. (*a*) Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart: II. The Ventricles, Phil. Tr. Roy. Soc., London, s. B **206**:181, 1915. (*b*) Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart: III. The Dog's Ventricle, ibid. **207**:247, 1916; (*c*) The Spread of the Excitatory Process in the Vertebrate Heart, ibid. **207**:221, 1916.

tion directed upward (common type) in lead I was considered to represent right bundle branch block and a main QRS deflection directed downward in lead I (uncommon or rare type) was interpreted as left bundle branch block.

Interest in the problem spread to this country, and in 1916 Oppenheimer and Rothschild [9] studied 62 cases of intraventricular conduction defects, of which they considered 58 as examples of arborization block, an electrocardiographic pattern inscribed in the presence of diffuse myocardial disease involving the conduction system distal to the two main bundle branches. Carter [10] accepted this concept, adding it to his previous criteria, but pointed out that low voltage did not preclude the presence of block in the bundle branch itself. Willius [11] also published a report on a series of cases placed in this category. On the other hand, extensive subendocardial fibrosis produced by ligation of the coronary artery in the canine heart did not produce such patterns,[12] nor did cutting the subdivisions of the branches bridging the ventricular cavity.[12b] Failing to confirm experimentally the concept of arborization block, Wilson and Herrmann [12b] concluded that the conduction defect must be located in the bundle branch when the criteria of Carter were fulfilled and that a typical widened QRS complexes represented incomplete bundle branch block. This view was given strong support by the experiments of Stenström.[13]

The earliest inference that the orthodox classification was erroneous stemmed from the work of Boden and Neukirch [14] in 1918. They obtained a downwardly directed main ventricular complex in lead I after

9. Oppenheimer, B. S., and Rothschild, M. A.: Abnormalities in the QRS Group of the Electrocardiogram Associated with Myocardial Involvement, Proc. Soc. Exper. Biol. & Med. **14**:57, 1916; Electrocardiographic Changes Associated with Myocardial Involvement with Special Reference to Prognosis, J. A. M. A. **69**:429 (Aug. 11) 1917.

10. Carter, E. P.: Further Observations on the Aberrant Electrocardiograms Associated with Sclerosis of the Atrio-Ventricular Bundle Branches and Their Terminal Arborizations, Arch. Int. Med. **22**:331 (Sept.) 1918.

11. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

12. (*a*) Smith, F. M.: Experimental Observations on the Atypical Q-R-S Waves of the Electrocardiogram of the Dog, Arch. Int. Med. **26**:205 (Aug.) 1920. (*b*) Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, ibid. **26**:153 (Aug.) 1920.

13. Stenström, N.: (*a*) Contributions to the Knowledge of Incomplete Bundle Branch Block, Acta med. Scandinav. **57**:385, 1922; (*b*) An Experimental and Clinical Study of Incomplete Bundle Branch Block, ibid. **60**:552, 1924; (*c*) Further Experience on Incomplete Bundle Branch Block in Man, ibid. **67**:353, 1927.

14. Boden, E., and Neukirch, P.: Elektrokardiographische Studien am isolierten Säugetier- und Menschenherzen bei direkter und indirekter Ableitung, Arch. f. d. ges. Physiol. **171**:146, 1918.

excision of the right ventricle and an upwardly directed main deflection in lead I after excision of the left ventricle in perfused canine and human hearts. Two years later, Oppenheimer and Pardee [15] observed histologic lesions in the branch opposite the expected one in 2 cases. That same year (1920), in a theoretic analysis of the electrocardiogram, Fahr [16] arrived at the correct conclusion that the orthodox interpretation of the site of bundle branch block should be reversed, and this view was supported by the monocardiographic analysis of Mann.[17] Despite these unexpected reports the old classification persisted in the clinical reports which appeared during the ensuing decade,[18] and Willius [19] classified intraventricular block in 1929 into right complete bundle branch block as the common type, left complete bundle branch block as the uncommon or rare type and incomplete bundle branch block as atypical widened QRS complexes with duration of 0.1 second or more.

The sparse opposition to this point of view received considerable support from the studies of Barker, Wilson and associates [20] performed on a patient whose heart was exposed after an operation for drainage of purulent pericarditis. They noted that premature systoles originating in the left ventricle elicited downwardly directed QRS deflections in lead I and those from the right ventricle had an opposite effect. By inference they concluded that the "common" type was due to left and the "uncom-

15. Oppenheimer, B. S., and Pardee, H. E. B.: The Site of the Cardiac Lesion in 2 Instances of Intraventricular Heart Block, Proc. Soc. Exper. Biol. & Med. **17**:177, 1920.

16. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920.

17. Mann, H.: A Method of Analyzing the Electrocardiogram, Arch. Int. Med. **25**:283 (March) 1920.

18. Herrick, J. B., and Smith, F. M.: Clinical Observations on Block of the Branches of the Auriculo-Ventricular Bundle, Am. J. M. Sc. **164**:469, 1922. White, P. D., and Viko, L.: Clinical Observations on Heart Block, ibid. **165**:659, 1923. Hart, T. S.: Block of the Branches of the Bundle of His: Clinical Notes on Changes Following Administration of Digitalis, Arch. Int. Med. **35**:115 (Jan.) 1925. Talley, J. E., and Reed, O. K.: A Study of 28 Cases of Bundle Branch Block, Am. Heart J. **1**:262, 1926. Willius, F. A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle Branch Block, ibid. **1**:576, 1926. Cowan, J., and Bramwell, J. C.: Clinical Aspects of Bundle Branch Block, Quart. J. Med. **19**:95, 1925. Bach, F.: On the Clinical Significance of Right Bundle Branch Block, ibid. **23**:261, 1930.

19. Willius, F. A.: Clinical Electrocardiograms: Their Interpretation and Significance, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1929.

20. Barker, P. S.; MacLeod, A. G.; Alexander, J., and Wilson, F. N.: The Excitatory Process in the Exposed Human Heart, Tr. A. Am. Physicians **44**:125, 1929. Barker, P. S.; MacLeod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, Am. Heart J. **5**:720, 1930.

mon" to right bundle branch block. However, continued support of the older European concept was offered by the elaborate analysis made by Fenichel in 1932 [21] and by the histologic studies of Mahaim.[22] The same year, however, Wilson and his associates [23] severed the bundle branches in dogs and demonstrated that their previous conclusions were correct. Serial precordial leads were utilized [24] to demonstrate a delay in the activation of the free wall of the homolateral ventricle (new classification) in the presence of bundle branch block in both dogs and man. By critical analysis, certain assumptions on which Lewis had based his determinations were shown to be unsound.[25] Nevertheless, Rothberger [26] continued to defend the earlier views and cited the need for more extensive histologic investigations in human hearts with intraventricular block. One such study [27] favored the new classification, but most of the ensuing reports were clinical analyses.[28]

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21. Fenichel, N. M.: An Analysis of the QRS Complex of the Electrocardiogram, Am. Heart J. **7**:514, 1932.

22. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara: Les syndromes coronaires, Paris, Masson & Cie, 1931.

23. (*a*) Wilson, F. N.; MacLeod, A. G., and Barker, P. S.: The Interpretation of Initial Deflections of the Ventricular Complex of the Electrocardiogram, Am. Heart J. **6**:637, 1931; (*b*) The Order of Ventricular Excitation in Human Bundle Branch Block, ibid. **7**:305, 1932.

24. (*a*) Wilson, F. N.; Johnston, F. D.; Hill, I. G. W.; MacLeod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, Am. Heart J. **9**:459, 1934. (*b*) Wilson and others.[23b]

25. Robb, J. S.; Easby, M., and Hiss, J. G. F.: Experimental Interference with Conduction in the Heart, Am. J. M. Sc. **188**:835, 1934. Wilson and others.[23a]

26. Rothberger, W.: Zur Diagnose des Schenkelblocks, Ztschr. f. klin. Med. **123**:460, 1933.

27. Oppenheimer, B. S., and Oppenheimer, E.: The Site of the Cardiac Lesion in 10 Cases of Intraventricular Block Including Bundle Branch Block and Arborization Block, Tr. A. Am. Physicians **45**:427, 1930.

28. Hill, I. G. W.: Bundle Branch Block: A Clinical and Histological Study, Quart. J. Med. **24**:15, 1930. Campbell, S. B. B., and Turkington, S. I.: Right Bundle Branch Block: An Analysis of the Clinical Records of 56 Cases with Typical Electrocardiograms, ibid. **24**:481, 1931. Smith, A. L.: A Review of 47 Cases of One-Sided Branch Block, Nebraska M. J. **17**:179, 1932. Tung, C. L., and Cheer, S. N.: A Correlation of Clinical and Electrocardiographic Findings in Human Bundle Branch Block, Chinese M. J. **47**:15, 1933. King, J. T.: Bundle Branch Block: A Case Analysis with Especial Reference to Incidence and to Prognosis, Am. J. M. Sc. **187**:149, 1934. Wood, F. C.; Jeffers, W. A., and Wolferth, C. C.: Follow-Up Study of 64 Patients with a Right Bundle Branch Conduction Defect, Am. Heart J. **10**:1056, 1935. Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Lesions, Am. J. M. Sc. **191**:88, 1936. Edeiken, J., and Wolferth, C. C.: Clinical Significance of the M or W-Shaped QRS Complex in Lead II of the Electrocardiogram, ibid. **188**:842, 1934.

Abundant experimental confirmation of the new classification followed, however. Mann [29] in 1931 again employed the monocardiogram (a method of fusing the three standard limb leads into one resultant simple curve) to support it. Further confirmation was obtained from the patterns observed after section of the bundle branches in the cat [30] and in the monkey [31] and from the form of premature systoles elicited from exposed animal and human hearts.[32]

Other methods were introduced for the study of this problem. Eppinger and Rothberger [28] noted a delay in the pulse wave coming from the injured ventricle. Various methods were employed to study this asynchronism of ventricular ejection occurring in the presence of intraventricular block, including electrocardiograms taken simultaneously with stethograms, arterial sphygmograms and roentgen kymograms of the great vessels.[33] The correlation between later ejection of the left ventricle and the common type of intraventricular block was usually, but not invariably, present.[33c] It was pointed out, however, that intraventricular block

29. Mann, H.: Interpretation of Bundle Branch Block by Means of the Monocardiogram, Am. Heart J. **6**:447, 1931.

30. Roberts, G. H.; Crawford, J. H.; Abramson, D. I., and Cardwell, J. C.: Experimental Bundle Branch Block in the Cat, Am. Heart J. **7**:505, 1932.

31. Roberts, G. H.; Crawford, J. H., and Abramson, D. I.: Experimental Bundle Branch Block in the Monkey, J. Clin. Investigation **14**:867, 1935.

32. (*a*) Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricle, Am. Heart J. **7**:471, 1932. (*b*) Lundy, C. J., and Bacon, C. M.: Premature Left Ventricular Beats from Electrical Stimulation of Exposed Human Heart, Arch. Int. Med. **52**:30 (July) 1933. (*c*) Vander Veer, J. B.: Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, Am. Heart J. **8**:807, 1933. (*d*) Kountz, W. B.; Prinzmetal, M.; Pearson, E. F., and Koenig, K. F.: The Effect of Position of the Heart on the Electrocardiogram, ibid. **10**:605, 1935. (*e*) Kountz, W. B.; Prinzmetal, M., and Smith, J. R.: The Effect of Position of the Heart on the Electrocardiogram: Observations upon the Electrocardiogram in the Monkey, ibid. **10**:623, 1935. (*f*) Marcou, I.: Experimental Extrasystoles Elicited Through Artificial Stimulation of the Endocardium of the Dog, ibid. **12**:301, 1936.

33. (*a*) Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricle in the So-Called Common Type of Bundle Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**:425, 1935. (*b*) Braun-Menendez, E., and Solari, L. A.: Ventricular Asynchronism in Bundle Branch Block, Arch. Int. Med. **63**:830 (May) 1939. (*c*) Katz, L. N.; Landt, H., and Bohning, A.: The Delay in the Onset of Ejection of the Left Ventricle in Bundle Branch Block, Am. Heart J. **10**:681, 1935. (*d*) Hirsch, I. S., and Gubner, R.: Application of Roentgenkymography to the Study of Normal and Abnormal Cardiac Physiology, ibid. **12**:413, 1936. (*e*) Nichol, A. D.: Interpretation of Lead Inversion in Bundle Branch Block, ibid. **9**:72, 1933. (*f*) Groedel, F. M.: Physiological and Pathological Asynchronism of the Function of the Heart Chambers, Exper. Med. & Surg. **2**:352, 1944. (*g*) Krumbhaar, E.: Transient Heart Block: Electrocardiographic Studies, Arch. Int. Med. **19**:750 (May) 1917.

can exist without detectable asynchronism of ejection.[33b] Recently, electrokymographic studies have demonstrated slight asynchronism of ventricular ejection in 54 of 68 normal persons, with abnormal delays in ejection in patients with intraventricular block (according to the new classification).[34]

Wilson and associates later described the so-called S type as a manifestation of right bundle branch block.[24a] Further attempts at classification based on the newer point of view were set forth by Graybiel and Sprague in 1933,[35] Bayley [36] and others.[37] However, as was pointed out,[38] "The classifications . . . do not appear to dispel the mist which surrounds the bundle branch concept."

The study of the pattern of intraventricular block and premature systoles by esophageal leads,[39] by endocardiac leads in dogs,[32f] by intracavity leads in human beings [40] and by axonometry [41] confirmed the fact

34. Ellinger, G. F.; Gellick, F. G.; Boone, B. R., and Chamberlain, W. E.: Electrokymographic Studies of Asynchronism of Ejection from the Ventricles, Am. Heart J. **35**:971, 1948.

35. Graybiel, A., and Sprague, H. B.: Bundle Branch Block: Analysis of 395 Cases, Am. J. M. Sc. **185**:395, 1933.

36. Bayley, R. H.: The Frequency and Significance of Right Bundle Branch Block, Am. J. M. Sc. **188**:236, 1934.

37. (*a*) Freund, H. A., and Sokolov, R.: Bundle Branch Block: Criteria of Classification, Diagnosis and Prognosis; A Study of 210 Cases with Follow-Up Data, Arch. Int. Med. **63**:318 (Feb.) 1939. (*b*) Reeser, R., Jr.; Willius, F. A., and Dry, T. J.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complexes of the Electrocardiogram: II. Special Consideration of Bundle Branch Block with Concordant Graphs and with Discordant Graphs, ibid. **67**:1027 (May) 1941. (*c*) Dry, T. J.; Willius, F. A., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: III. Special Considerations of the Wide S Wave Pattern, with Report of 3 Cases, ibid. **67**:1034 (May) 1941. (*d*) Katz, L. N.: Electrocardiography Including an Atlas of Electrocardiograms, ed. 2, Philadelphia, Lea & Febiger, 1946.

38. Glomset, D. J.; Glomset, A. T. A., and Birge, R. F.: Morphologic Study of the Cardiac Conduction System: III. Bundle Branch Block, Am. Heart J. **28**:348, 1944.

39. Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography: I. The Application of the Esophageal Lead to Human Subjects with Observations on the Ta Wave, Extrasystoles and Bundle Branch Block, Am. Heart J. **12**:1, 1936.

40. Sodi Pallares, D.; Vizcaino, M.; Soberon, J., and Cabrera Cosio, E.: Comparative Study of the Intracavity Potential in Man and in the Dog, Am. Heart J. **33**:819, 1947. Hecht, H. H.: Potential Variations of Right Auricle and Ventricular Cavities in Man, ibid. **32**:39, 1946. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiograms Obtained by Heart Catheterization in Man, ibid. **33**:604, 1947. Sodi Pallares, D.; Thomsen, P., and Soberon, J.: New Contribution to the Study of the Intracavity Potential in Cases of Right Bundle Branch Block in the Human Heart, ibid. **36**:1, 1948.

41. Zarday, I.: A propos de la localisation électrocardiographique des blocs de branche, Acta cardiol. **4**:342, 1949.

that, in most instances, the presence of a broad upright deflection in lead I (common type) is associated with a conduction disturbance in the left ventricle and that the presence of a prominent broad S wave in lead I indicates a conduction disturbance in the right ventricle. The duration of the QRS complex in intraventricular block is generally accepted as being 0.12 second or more in the limb leads.[37d] Neuhof [42] expressed the opinion that a QRS interval measuring over 0.07 second in adults indicated myocardial disease, but McGinn and White [43] in a statistical study of a large number of normal persons set the upper limit of the normal QRS interval at 0.10 second in the adult and 0.09 second in the child under the age of 12 years. Wilson [44] pointed out that complete right bundle branch block may be present with a QRS interval measuring as little as 0.10 second in the limb leads, whereas complete left bundle branch block is present only when the interval measures 0.12 second or more.

EFFECT OF "ELECTRICAL" POSITION ON PATTERN AND ELECTRICAL AXIS OF INTRAVENTRICULAR BLOCK

Einthoven and associates [45] early recognized that positional change of the heart led to an altered QRS pattern. Boden and Neukirch [14] also observed profound changes in the form, amplitude and direction of the QRS deflections after rotating the perfused heart on various axes, and these effects were confirmed by others.[46] Lewis [47] noted an altered electrical axis even with respiratory changes in heart position. Einthoven stated his belief that the anatomic and electrical axes rotated similarly and equally, but Lewis reported that even small rotations on an anatomic long axis caused definite rotation of the electrical axis. The latter

42. Neuhof, S.: The Clinical Significance of the Abnormally Wide Ventricular Deflection in the Electrocardiogram, Arch. Int. Med. **22**:45 (July) 1918.

43. McGinn, S., and White, P. D.: The Duration of the QRS Complex in the Normal and in the Abnormal Electrocardiogram, Am. Heart J. **9**:642, 1934.

44. Wilson, F. N.: Concerning the Form of the QRS Deflection of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**:1110, 1942.

45. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.

46. Waller, A. D.: The Various Inclinations of the Electrical Axis of the Human Heart, Proc. Roy. Soc. London, s. B **88**:49, 1914. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, Am. J. M. Sc. **156**:17, 1918. Cohn, A. E.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:312, 1922.

47. Lewis, T.: Movements of the Heart's Axis with Respiration, Heart **10**:257, 1923.

observations were confirmed by Meek and Wilson in 1926[48] and later by Nathanson.[49] The effect of altering the position of the heart on the configuration of the QRS complex obtained in intraventricular block and premature systoles was first pointed out by Katz and his co-workers. They noted profound changes in the direction and pattern of the QRS complex following altered anatomic position in both human[50] and canine hearts.[51] The degree of alteration depended on the type of anatomic rotation present. This led to the natural conclusion that the site of block or premature systoles could not be located with certainty from the limb lead pattern and that intraventricular block should be classified only in descriptive terms.[37d] These observations were repeatedly confirmed, [52] but it was the opinion of the later investigators that the block could still be located in either right or left ventricle from the limb lead pattern, since they were of the view that the degree of rotation required to reverse the direction of the QRS complex was greater than would obtain clinically. Credence seems to be lent to this view by the recent observations of Wendt,[53] who attempted to simulate cardiac rotations by changing the position of the Einthoven triangle in reference to the heart.

The utilization of V and aV extremity leads ("unipolar") leaves little doubt that the limb lead pattern in intraventicular conduction defects is determined by the "electrical" position of the heart, as well as by the location of the conduction defect,[54] thus substantiating the con-

48. Meek, W., and Wilson, A.: The Effect of Changes in Position of the Heart on the Q-R-S Complex of the Electrocardiogram, Arch. Int. Med. **36**:614 (Nov.) 1925.

49. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart with Changes of Posture, Proc. Soc. Exper. Biol. & Med. **28**:766, 1931.

50. Kissin, M.; Ackerman, W., and Katz, L. N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle Branch Block in Man, Am. J. M. Sc. **186**:721, 1933.

51. Katz, L. N., and Ackerman, W.: The Effects of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, J. Clin. Investigation **11**:1221, 1932. Ackerman, W., and Katz, L. N.: Reversal in Direction of the QRS Complex of Experimental Right Bundle Branch Block with Change in the Heart's Position, Am. Heart J. **8**:490, 1933.

52. (*a*) Footnote 32 *c* to *e*. (*b*) Foster, P. C.: The Relation of the Position of the Heart to the Initial Ventricular Deflection in Experimental Bundle Branch Block, Am. Heart J. **10**:1042, 1935. (*c*) Lundy, C. J.; Treiger, I., and Davison, R.: Ventricular Extrasystoles Induced by Electrical Stimulation of the Exposed Human Heart Rotated 30 Degrees Counterclockwise on Its Vertical Axis, ibid. **17**:85, 1939.

53. Wendt, L.: Ueber die elektrokardiographische Differentialdiagnose zwischen Schenkel und Verzweigungsblock, Klin. Wchnschr. **24-25**:307, 1947.

54. (*a*) Wilson.[44] (*b*) Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F.; Erlanger, H.; Kossman, C. E.; Hecht, H. H.; Cotrim, N.; Menezes, R.; Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944. (*c*) Goldberger, E.: The Basic Electrocardiographic Pattern in Bundle Branch Block, J. Lab. & Clin. Med. **30**:220, 1945.

tentions of Katz and his associates.[55] Recent studies by Jones and Feil[56] and others[57] on the effects of postural changes on the pattern of intraventricular block confirmed the views that pronounced changes occur in the limb leads with altered intrathoracic position of the heart. Just as striking was the absence of significant changes in the precordial leads, an observation previously made in instances of normal intraventricular conduction.[58] The changes in "electrical" position which do occur are often of greater magnitude than the anatomic change.[47] Thus, rather simple postural changes occurring in everyday circumstances will produce significant changes in the limb lead pattern. However, it has been well shown that the time of onset of the "intrinsicoid" deflection and the pattern inscribed in lead V_1 in comparison with that in lead V_5 or V_6 will almost always permit localization of the block to the right or left ventricle.[59]

That early studies did not properly localize the site of block[60] was due to a failure to recognize the role played by "electrical" position of the heart. The canine heart is usually in a semivertical position, whereas the human heart is more transversely placed in the thorax. Thus, the QRS pattern in lead V_5 will resemble the deflections in leads II and III in the canine electrocardiogram, whereas a similar pattern appears in lead I in the human curve in most instances of intraventricular block.[44]

The early studies on this subject[61] led to the view that the development of intraventricular block was associated with striking changes in the direction of the electrical axis as measured by the method of Einthoven. Fahr[16] was apparently the first to question this, arriving at opposite conclusions in a theoretic analysis. It has since been demonstrated that the axis shift is not significantly changed with the onset of block.[57] Luten and Grove,[62] and later Hyman and Parsonnet,[63] observed an

55. Kissin and others.[50] Katz and Ackerman. [51]

56. Jones, A. M., and Feil, H.: The Effect of Posture upon Axis Deviation in Human Bundle Branch Block, Am. Heart J. **16**:739, 1948.

57. Jervell, O., and Orning, K.: Changes in the Axis Deviation in Bundle Branch Block with Changes of Heart Position, Cardiologia **14**:295, 1949.

58. Stewart, H. J., and Bailey, R. L.: The Effect of Position on the Form of Precordial Leads of the Electrocardiogram, Am. Heart J. **18**:271, 1939.

59. Wilson and others.[54] Jones and Feil. [56] Jervell and Orning. [57]

60. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925.

61. Eppinger and Rothberger.[2a] Lewis.[6b, c] Wilson and Herrmann.[12b]

62. Luten, E., and Grove, E.: The Incidence and Significance of Electrocardiograms Showing Features of Left Axis Deviation and QRS of Normal Duration with Inverted T_1 and Upright T_3, Am. Heart J. **4**:431, 1929.

63. Hyman, A. S., and Parsonnet, A. E.: Bundle Branch Block: The Phenomenon of Its Development in Relation to Axis Deviation of Heart, Arch. Int. Med. **45**:868 (June) 1930.

absence of axis shift in cases of block in which previous records revealed normal conduction. Many similar instances have been cited in further confirmation.[64] The recent study of axis shift in human cases of block by Jones and Feil [65] leaves little doubt that the onset of intraventricular block does not cause significant changes in electrical axis. When such changes do occasionally occur, they are in the same direction, respectively. It is clear, then, that the electrical axis noted in intraventricular block is due principally to the axis position present prior to the onset of block.[66]

The concept of electrical axis as set forth by Einthoven has been seriously questioned by competent investigators.[67] Wolferth and Livezey [67c] studied records of patients with transient right and left block in whom there were rapid transitions from normal to abnormal conduction in one or more leads. They concluded that the levocardiogram must contribute almost solely to the QRS complex in the limb leads and the left-sided precordial leads. The dextrocardiogram appeared to exert a significant influence only in leads taken from the immediate vicinity of the right ventricle. This evidence, in their opinion, raised serious questions about the role of the potential variations developed during activation of the right and left ventricles in the hypothesis of the electrical axis; it was offered in support of the contention of Katz [67d] that there is a favored avenue of conduction between the heart and extremities and that the electrocardiogram records events in certain favored areas of the myocardium rather than the balance of electromotive forces developed from moment to moment in the entire heart. The extensive analysis of Myers and Klein [68] confirmed the fact that the potential variations recorded by each limb electrode usually resemble those at certain positions on the precordium.

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64. (*a*) Kurtz, C. M.: Transient Complete Bundle Branch Block, Am. Heart J. **11**:212, 1936. (*b*) Comeau, W. J.; Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated with Heart Disease, ibid. **15**:276, 1938.

65. Jones, A. M., and Feil, H.: On Axis Deviation in Human Bundle Branch Block, Am. Heart J. **36**:98, 1948.

66. Zarday.[41] Jervell and Orning.[57]. Kurtz.[64a] Jones and Feil.[65]

67. (*a*) Katz.[57d] (*b*) Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, Am. J. M. Sc. **203**:641, 1942. (*c*) Wolferth, C. C., and Livezey, M. M.: Observations on Changes in Ventricular Complexes Produced by Bundle Branch Block with Special Reference to the Hypothesis of Electrical Axis and the Concept of the Dextrocardiogram and Levocardiogram, Am. Heart J. **34**:1, 1947. (*d*) Katz, L. N.: Concerning a New Concept of the Genesis of the Electrocardiogram, ibid. **13**:17, 1937.

68. Myers, G. D., and Klein, H. A.: The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads, Am. Heart J. **35**:727, 1948.

HISTOLOGIC STUDIES OF THE CONDUCTION SYSTEM IN INTRAVENTRICULAR BLOCK

A significant lack of correlation has been observed between the anatomic site of block and the electrocardiographic localization. This is partly due to the difficulties involved in visualizing grossly and in making serial sections of the conduction system, explaining the paucity of adequate histologic studies in human cases of intraventricular block. Part of this discrepancy may be attributed to the sole use of the limb leads in electrocardiographic localization.

Eppinger and Stoerck [4] noted lesions in the right bundle branch with none in the left in 2 instances of the common type of block (left). Cohn and Lewis [69] were unable to find any lesions in 4 cases, considering them as functional in origin. Oppenheimer and Rothschild [9] reported widespread subendocardial fibrosis in 58 cases of intraventricular block. Later, Oppenheimer and Pardee [15] saw lesions in 2 cases, and in 1930 Oppenheimer and Oppenheimer reported finding lesions in 10 cases in the homolateral ventricle (new classification).[27] The observation of lesions in the homolateral ventricle was also described by Lewis,[60] Taussig,[70] Hill,[71] Wolferth and associates [72] and Herles and his co-workers.[73] Mahaim [22] carefully studied the data in 19 cases previously reported by others and concluded that only 4 were acceptable, the lesions in these all being encountered in the opposite bundle branch (new classification). He also studied extensively 7 cases of his own and reported lesions in both bundle branches. He pointed out that perforating branches of the anterior descending coronary artery usually supplied both the right and the anterior divisions of the left bundle branch, whereas perforating branches of the posterior descending coronary artery supplied the auriculoventricular node, common bundle and the posterior division of the left branch. Because of this vascularization he was of the view that unilateral lesions would be unusual and his own studies supported this contention. Rosenthal [74] likewise noted lesions in the left branch in 1 case of right-sided block. Yater and

69. Cohn, A. E., and Lewis, T.: The Pathology of Bundle Branch Lesions of the Heart, Proc. New York Path. Soc. **14**:207, 1914.

70. Taussig, H. B.: A Case of Bundle Branch Block Confirmed by Pathological Study, Bull. Johns Hopkins Hosp. **45**:45, 1929.

71. Hill, I. G. W.: Bundle Branch Block: A Clinical and Histological Study, Quart. J. Med. **24**:15, 1930.

72. Wolferth, C. C.; Margolies, A., and Bellet, S.: The Side of the Significant Lesions in the Common Type of Bundle Branch Block, Tr. A. Am. Physicians **48**:187, 1933.

73. Herles, V. F.; Lukl, P.; Prusik, B., and Sikl, H.: Zur Frage der Lokalisation des Schenkelblocks, Cardiologia **2**:1, 1938.

74. Rosenthal, S. R.: Branch Arborization and Complete Heart Block, Arch. Int. Med. **50**:730 (Nov.) 1932.

associates [75] emphasized again that unilateral lesions were unusual and extensive studies of 6 hearts [76] revealed lesions bilaterally, although they were severer in the homolateral bundle branch, according to the new classification. Evans and Turnbull [77] studied an instance of S type block, observing lesions in both branches, but again more extensive in the right one. The Glomsets [78] reviewed this subject and noted that in 22 cases of the common type of block reported in the literature there were no lesions in about 25 per cent of the cases; blocking lesions were demonstrated in the left bundle branch in about one third of the cases and in the right in the others.

It is apparent that blocking lesions, when present, are usually bilateral. It is also clear that histologic studies have contributed little, perhaps serving to confuse the subject. The most recent histologic studies [78] have again given confusing results.

CLINICAL STUDIES

The early studies of intraventricular block led to its association with advanced heart disease and a grave prognosis, especially when combined with low voltage.[79] This association persisted throughout the earlier clinical studies.[80] Later it became apparent that the prognosis in intraventricular block was that of the underlying heart disease and not dependent on the type of block present.[81]

Early studies contributed to the belief that the uncommon type (right) was a rare occurrence, but later statistical studies [80] revealed right-sided block to be of frequent occurrence if the S type was included.[82] Left branch block may occur in slightly greater frequency than right because disease of the left ventricle is commoner.[83] Intra-

75. Yater, W. M.; Cornell, V. H., and Claytor, T.: Auriculoventricular Heart Block Due to Bilateral Bundle-Branch Lesions, Arch. Int. Med. **57**:132 (Jan.) 1936.

76. (*a*) Yater, W. M.: The Morbid Anatomy of Bundle Branch Block, M. Ann. District of Columbia **7**:10, 1938; (*b*) Pathogenesis of Bundle Branch Block, Arch. Int. Med. **62**:1 (July) 1938.

77. Evans, W., and Turnbull, H. M.: The Newer Electrocardiogram Denoting Right Bundle-Branch Block, Lancet **2**:1127, 1937.

78. Aberle, L., and Foldvary, G. A.: Recent Observations on the Subject of Bundle Branch Block, Orvosi hetil. **89**:438, 1948. Lenègre, J., and Chevalier, H.: Étude anatomo-clinique électrique et histologique d'un nouveau cas de bloc typique de la branche gauche, Arch. d. mal. du cœur **42**:197, 1949.

79. Oppenheimer and Rothschild.[9] Carter.[10] Willius.[11]

80. Footnotes 18 and 28.

81. Graybiel and Sprague.[35] Reeser and others.[37b]

82. (*a*) Sodi Pallares, D.; Brumlik, J.; Mendoza, F., and Cabrera, E.: Estudio de 125 Casos de Bloqueo de Rama, Arch. Inst. cardiol. México **15**:241, 1945. (*b*) Pick, A.: Beitrag zur Frage des atypischen Schenkelblocks, Ztschr. f. klin. Med. **129**:719, 1936.

83. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944.

ventricular block is noted generally in clinical practice and is usually permanent, once it has appeared. The occasional reported instances of intermittent and transient block were almost invariably associated with underlying heart disease and usually later became permanent.[64b]

Intraventricular block commonly occurs in diseased hearts.[84] Rarely it can be a congenital anomaly of the conduction system associated with septal or other defects, and in a few cases it is an isolated abnormality.[85] In more than 80 per cent of cases the underlying basis is hypertensive vascular disease and arteriosclerosis.[86] About 10 per cent of cases occur in chronic rheumatic heart disease. In occasional cases, intraventricular block has been associated with myocarditis due to diphtheria, acute rheumatic carditis, syphilitic gummas of the septum, subacute bacterial endocarditis, tumors of the myocardium and trauma.[87] It has been reported as a transient phenomenon in persons without heart disease,[85c] after prolonged rapid heart rates,[60] congestive failure [88] and shock,[89] after toxic doses of digitalis and quinidine,[54b] following vagal stimulation [64b] and with acute cor pulmonale.[82b] There have been interesting but rare instances of block due to sensitivity to acetylsalicylic acid,[90] malnutrition,[91] fatty infiltration of the septum [92] and calcification in the septum [93] and during exercise in patients with coronary sclerosis.[94]

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84. Bohning, A.; Katz, L. N.; Langendorf, R., and Blumenthal, B.: Intraventricular Block, Including So-Called Bundle Branch Block, Am. J. M. Sc. **202**:671, 1941.

85. (*a*) Dry and others.[87c] (*b*) Langley, R. W.; Reed, J. C., and Utz, D. C.: Bundle Branch Block: A Review of 100 Cases, Am. Heart J. **33**:730, 1947. (*c*) von Deesten, H. T., and Dolganos, M.: Atypical Bundle-Branch Block with a Favorable Prognosis, Am. J. M. Sc. **188**:231, 1934.

86. (*a*) White.[83] (*b*) East, C. F. T., and Bain, C. W. C.: Recent Advances in Cardiology, ed. 4, Philadelphia, The Blakiston Company, 1948.

87. (*a*) White.[83] (*b*) Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1945.

88. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Function Changes in the Heart, Arch. Int. Med. **18**:830 (Dec.) 1916.

89. Morris, R. S., and McGuire, J.: Transient Complete Bundle Branch Block, Am. J. M. Sc. **184**:202, 1932.

90. Bloom, N., and Walker, H.: Nodal Rhythm and Bundle Branch Block Following Aspirin Sensitivity, J. Lab. & Clin. Med. **29**:595, 1944.

91. Braun, K.; Roth, I., and Suesskind, S.: Intraventricular Block in Malnutrition and Vitamin B Deficiency, J. Pediat. **30**:177, 1947.

92. Spain, D. M., and Cathcart, R. T.: Heart Block Caused by Fat Infiltration of the Interventricular Septum (Cor Adiposum), Am. Heart J. **32**:659, 1946.

93. Windholz, F., and Grayson, C.: Roentgen Demonstration of Calcifications in the Interventricular Septum in Cases of Heart Block, Am. J. Roentgenol. **58**:411, 1947.

94. Donath, F., cited by Dressler, W., and Roesler, H.: An Atlas of Electrocardiography, Springfield, Ill., Charles C Thomas, Publisher, 1949.

Intraventricular block is about three times as common in men [95] as in women, and more than 80 per cent of the patients are over 50 years old.[96] The prognosis after the appearance of intraventricular block is related to the underlying heart disease.[97] The average survival after the discovery of left intraventricular block is one to two years, but there are many exceptions.[97b] With the observation of such cases over long periods it is apparent that even in the presence of underlying heart disease the prognosis must be individualized.[98] It is widely held that the prognosis is more serious with left-sided block.[99] Extensive statistics have not been compiled in this regard and there is disagreement in those reported.[100] However, it seems probable, since most instances of block occurring in the absence of heart disease are of the right-sided type.[85c] It is clear that the patient, and not the electrocardiogram, must be evaluated in the presence of intraventricular block and that emphasis should be given to the realization that intraventricular block occurs in patients who may live many years after its appearance and in persons with no other evidence of heart disease.[99b]

CLINICAL AND DYNAMIC MANIFESTATIONS OF INTRAVENTRICULAR BLOCK

Intraventricular block is essentially an electrocardiographic diagnosis. No symptoms can be related to the conduction defect itself, as demonstrated by the lack of development of symptoms in patients in whom the block appears transiently.[101] The symptoms present are those of the underlying heart disease.[83]

It has been shown that slight asynchronism of ventricular ejection is often present in normal human beings [84] and that there is a more pronounced asynchronism in patients with intraventricular block, with a delayed ejection from the affected ventricle.[102] Such asynchronism of ejection and valvular opening and closing might cause certain signs

95. White.[83] Bohning and others.[84]

96. Bohning and others.[84] Levine.[87]

97. (*a*) Footnote 37 *a* and *b*. (*b*) Kaplan, L. G., and Katz, L. N.: The Prognosis of Intraventricular Block, Am. Heart J. **18**:145, 1939.

98. Langley and others.[85b] Pick.[82b]

99. (*a*) Dry and others.[87c] (*b*) Fisch, C.: Bundle Branch Block of the Broad S Type: Report of 11 Cases Without Any Evidence of Heart Disease with One Instance Showing Partial and Transient Block, J. Indiana M. A. **40**:1128, 1947.

100. Freund and Sokolov.[87a] Kaplan and Katz.[97b] Perera, G. A.; Levine, S. A., and Erlanger, H.: Prognosis of Right Bundle Branch Block: A Study of 104 Cases, Brit. Heart J. **4**:35, 1942.

101. Willius, F. A., and Anderson, M. J.: Transient, Recurrent, Complete Bundle Branch Block, Am. Heart J. **10**:248, 1934.

102. Footnote 33. Ellinger and others.[84] Wolferth and others.[72]

to lead the examiner to suspect the presence of an intraventricular block. Thus, diastolic gallop rhythm and reduplication of heart sounds may be heard. The latter may take the form of reduplicated apical sounds,[83] a prolonged first and split second sound at the second and third left interspaces or an abnormally long or split apical impulse.[103] The presence of reduplicated sounds and diastolic gallop, particularly when the heart rate is less than 90, is strongly suggestive of intraventricular block.[86b] Cardiomegaly[104] is common and pulsus alternans[87b] may occur. Asynchronism may occasionally be observed with the fluoroscope or with the roentgen kymograph.[103] There appear to be no other dynamic effects due to the conduction defect per se.

INCONSTANT INTRAVENTRICULAR BLOCK

The pattern of intraventricular block may occasionally be seen in single beats in an electrocardiogram with regular sinus rhythm and with a normal duration for most of the QRS complexes (intermittent intraventricular block). These widened complexes may appear allorhythmically. In analogy to auriculoventricular block, such records are then designated as 2:1, 3:1, and so on, partial intraventricular block. The term transient intraventricular block refers to the presence of an intraventricular conduction defect throughout a single electrocardiogram, which, however, disappears in later records; if this pattern of delayed conduction is observed at different times in seriatim records, it is called recurrent intraventricular block. When this phenomenon is elicited by a change in heart rate, a functional factor related to the normal or a prolonged refractory period can be assumed.

The commonest type of block which can be considered as functional in origin is that occurring as a result of the normal refractory period of the bundle branches. Lewis[105] originally recognized this phenomenon in 1910 and later termed it aberrant ventricular response to supraventricular premature beats, due to functional bundle branch block. He noted it to be more readily observed when conduction was previously depressed by anoxemia.[60] Similar aberrant response was later recognized to occur in any type of rapid heart action, such as auricular flutter, fibrillation and tachycardia. The degree of aberrancy could be correlated with the degree of prematurity or the duration of the preceding

103. Luisada, A. A.: Heart: A Physiologic and Clinical Study of Cardio-Vascular Disease, Baltimore, William & Wilkins Company, 1948.

104. Wolferth and others.[72] Rasmussen, H., and Moe, T.: Pathogenesis of Left Bundle Branch Block, Brit. Heart J. **10**:141, 1948.

105. (*a*) Lewis, T.: Paroxysmal Tachycardia: The Result of Ectopic Impulse Formation, Heart **1**:262, 1909-1910; (*b*) Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature, ibid. **2**:23, 1910.

cardiac cycle [106] and carried no prognostic significance.[107] Palmer and White [107] reached similar conclusions with regard to paroxysmal supraventricular tachycardia, although others have expressed the view that widened QRS complexes are more readily observed in patients with underlying heart disease.[108] A recent critical study by Berliner and Lewithin [109] showed that the degree of prematurity is the major but may not be the sole factor in determining the aberrancy of the ventricular response in such records. Cohn and Lewis [69] stated that the absence of histologic blocking lesions in 4 cases of intraventricular block supported the concept of a functional origin of block in hearts with slow rates, as well as with rapid action, and they based the changes on "fatigue" of the conduction tissue. A supernormal phase of intraventricular conduction may explain this occurrence.[110]

Lewis [111] initially described transient block in the presence of organic heart disease. The influence of vagal action was promulgated by Wilson in 1915,[112] but it has since been realized that he was dealing with an instance of Wolff-Parkinson-White syndrome. Herrmann and Ashman [113] wrote that a vagal action may have been operative in 8 cases of transient block which appeared with exercise and disappeared after sustained deep inspiration. Instances have been cited [64b] in which vagal pressure elicited the pattern of block without altered heart rate,[64b] and transient patterns of block have appeared only during slower heart

106. Stenström.[18c] White, P. D., and Stevens, H. W.: Ventricular Response to Auricular Premature Beats and to Auricular Flutter, Arch. Int. Med. **18**:712 (Nov.) 1916. Gouaux, J. L., and Ashman, R.: Auricular Fibrillation with Aberration Simulating Ventricular Paroxysmal Tachycardia, Am. Heart J. **34**:366, 1947.

107. Palmer, R. S., and White, P. D.: The Clinical Significance of Aberrant Ventricular Response to Auricular Premature Beats and to Paroxysmal Auricular Tachycardia, Am. Heart J. **4**:157, 1928.

108. (*a*) Comeau and others.[64b] (*b*) Kisch, B., and Grishman, A.: Transient Intraventricular Conduction Defect, Exper. Med. & Surg. **2**:277, 1944. (*c*) Vesell, H.: Critical Rates in Ventricular Conduction: Unstable Bundle Branch Block, Am. J. M. Sc. **202**:198, 1941.

109. Berliner, K., and Lewithin, L. P.: Auricular Premature Systole: I. Aberration of the Ventricular Complex in the Electrocardiogram, Am. Heart J. **29**:449, 1945.

110. Scherf, D., and Scharf, M. M.: Supernormal Phase of Intraventricular Conduction, Am. Heart J. **36**:621, 1948.

111. Lewis, T.: Certain Apical Signs of Myocardial Involvement, Brit. M. J. **1**:484, 1913.

112. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008 (Dec.) 1915.

113. Herrmann, G. R., and Ashman, R.: Partial Bundle Branch Block: A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle Branch Block, Am. Heart J. **6**:375, 1931.

rates and in the presence of increased vagal tone.[114] However, vagal influence has not been demonstrated to affect bundle branch conduction in the normal dog.[115] The association of transient block with faster rates, a block which disappeared at a critical point with slowing, has been frequently reported.[116] Vesell [108c] pointed out that, "At a certain cardiac rate the equilibrium between normal ventricular conduction and block is so delicate that it is frequently disturbed and several changes back and forth may take place within the period of a minute or two." Usually vagal stimulation caused the block pattern to disappear.[117] It has been shown that the vagi do not have a direct effect on intraventricular conduction but rather a secondary effect following slowing of the heart rate, permitting better recovery of the conduction tissue.[118] In those instances in which vagal stimulation was said to have elicited the pattern of block, underlying heart disease was present.[119]

Hypoxemia has also been implicated in the mechanism of transient intraventricular block. The association of such a pattern with shock, pulmonary edema, pulmonary embolism and heart failure has been observed commonly.[120] Comeau and others [64b] reviewed 71 cases of

114. (*a*) Levine.[87b] (*b*) Holzmann, M.: Seltene Abarten von unbeständigen Schenkelblock, Cardiologia **7**:113, 1943. Baark, V.: Case of Intermittent Branch Block in a Patient with Myasthenia Gravis, Acta med. Scandinav. **121**:295, 1945.

115. Boyer, N. H.: Paroxysmal Bundle Branch Block Converted into Two-to-One Bundle Branch Block by Means of Atropine: Case Report, Am. Heart J. **18**:115, 1939.

116. (*a*) Comeau and others.[64b] (*b*) Willius and Anderson.[101] (*c*) Boyer.[115] (*d*) Robinson.[88] (*e*) Vesell.[108c] (*f*) Robinson, G. C.: The Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med. **24**:422 (Oct.) 1919. (*g*) Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927. (*h*) Leinbach, R. F., and White, P. D.: Two to One Right Bundle Branch Block, Am. Heart J. **3**:427, 1928, (*i*) Baker, B. M., Jr.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, Arch. Int. Med. **45**:814 (May) 1930. (*j*) Carter, E. P., and McEachern, D.: Recurrent Complete Heart Block, Bull. Johns Hopkins Hosp. **49**:337, 1931. (*k*) Elliot, A. H., and Nuzum, F. R.: Bundle Branch Block with Periods of Normal Intraventricular Conduction: Report of an Unusual Case, Am. Heart J. **7**:680, 1932. (*l*) Carr, F. B.: Functional Bundle Branch Block, New England J. Med. **209**:1101, 1933. (*m*) Sigler, L. H.: Functional Bundle Branch Block (Partial) Parodoxically Relieved by Vagal Stimulation, Am. J. M. Sc. **185**:211, 1933. (*n*) Cutts, F. B., and Roberts, C. P.: Two-to-One and Three-to-One Left Bundle Branch Block in the Presence of Auricular Flutter, Am. Heart J. **15**:501, 1938. (*o*) Eichert, H.: Transient Bundle Branch Block Associated with Tachycardia, ibid. **31**:511, 1946.

117. Footnote 116 *h* and *j* to *m*.

118. Boyer.[115] Robinson.[88] Robinson.[116f]

119. Comeau and others.[64b] Boyer.[115]

120. (*a*) Kurtz.[64a] (*b*) Robinson.[88] (*c*) Robinson.[116f] (*d*) Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle Branch Block, Am. Heart J. **2**:255, 1927. (*e*) Morris and McGuire.[89] (*f*) Durant, J. M.; Ginsburg, I. W., and Roesler, H.: Transient Bundle Branch Block and Other Electrocardiographic Changes in Pulmonary Embolism, Am. Heart J. **17**:423, 1939.

transient block and reported underlying heart disease in all but 6; disease of the coronary artery was present in 44, rheumatic heart disease in 6, diphtheria in 4, congenital heart disease in 1 and thyrotoxicosis in 3. The precipitating mechanism for the temporary appearance of block was occasionally myocardial infarction or angina pectoris, but in 25 instances it followed congestive heart failure. In most such cases, the pattern of block disappeared after rest in bed and digitalization.[121] Baker [116i] observed that in one instance the block, which had previously been present only at more rapid heart rates, failed to appear at these rates when oxygen was inhaled simultaneously. In others, oxygen administration was without effect.[116o] Intraventricular block was also observed to disappear after intravenous administration of aminophylline.[94] It has been shown that hypoxemia primarily affects auriculoventricular conduction and, in the normal heart, elicits relatively slight change in intraventricular conduction.[122] It is probable that the mechanism of the disappearance of intraventricular block induced by administration of oxygen or digitalization and rest in bed was merely slowing of the heart rate beyond a critical point, since slowing occurs with these procedures.[123]

The accumulation of acid metabolites during hypoxemia has also been implicated in such cases. Robinson [121] described instances of block associated with heart failure which disappeared with treatment and in his opinion such cases were due to a longer recovery time of the bundle branch secondary to accumulation of acid metabolites. There is some evidence lending credence to this concept. The disposal of acid metabolites has been shown to be incomplete and inefficient under conditions of poor oxygenation, and lactic acid formed in muscle had been observed to disappear in proportion to the oxygen supply.[124] Conduction delays have been elicited in the frog heart by adding lactic acid to the perfusion fluid.[125] Such a mechanism has also been invoked to explain the appearance of transient block present at more rapid heart rates and in the absence of heart failure.[126] However, the production of acid substances by activity of the conduction tissue has never been demonstrated.[116f]

121. Robinson.[88] Robinson.[116f]

122. Resnik, W. H.: Observations on the Effect of Anoxemia on the Heart: II. Intraventricular Conduction, J. Clin. Investigation **2**:117, 1925.

123. Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Observations on the Effects of Oxygen Therapy: II. Changes in the Circulation and Respiration, Am. J. M. Sc. **184**:810, 1932.

124. Fletcher, W. M., and Hopkins, F. G.: Lactic Acid in Amphibian Muscle, J. Physiol. **35**:247, 1907.

125. Burridge, W.: Propagation of Contraction in the Frog's Heart, J. Physiol. **45**:6, 1912.

126. Mines, G. R.: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:349, 1913.

Leinbach and White[116b] observed a patient with 2:1 partial intraventricular block which later became complete. They also cited a case of Stenström of a patient with 2:1 intraventricular block in whom normal conduction occurred at slower rates and complete block at more rapid rates. Similar instances of 2:1 to 4:1 partial block have been described,[127] even with Wenckebach periods.[114b] In certain cases intraventricular block was reported to be initially transient and later permanent,[128] and in rare instances left-sided block disappeared years after its appearance.[129]

Many other cases of transient and recurrent intraventricular block have been reported.[130] It is apparent that transient block often is the harbinger of permanent block and that underlying heart disease is usually present.[64] Superimposed on the latter, precipitating mechanisms leading to block include heart failure, rapid heart rate, coronary insufficiency with or without myocardial infarction, pulmonary embolism, uremia, anesthesia and shock. In certain instances, fibrosis has been observed in the bundle branches, and in others no lesions were noted.[64b] Carter and Dieuaide[131] pointed out that "a few intact fibers may under favorable circumstances serve to carry on the process normally, while some subtle local circulatory deficiency or a temporary increase in vagal action may result in failure of the few remaining fibers to function." Wilson and Herrmann[132] demonstrated that partial block in one of the bundle branches of the dog's heart, causing a delay in conduction of 0.04 second or more, led to an electrocardiographic pattern identical with that seen after complete interruption of the same bundle branch; thus, a

127. (*a*) Footnote 116 *g*, *k* and *n*. (*b*) Slater, S. R.: Partial Bundle-Branch Block: A Case of Three-to-One and Four-to-One Block, Am. Heart J. **5**:617, 1930. (*c*) Kelly, L. W.: Two to One Right Bundle Branch Block, ibid. **6**:285, 1930. (*d*) Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Partial Bundle Branch Block, ibid. **7**:753, 1931.

128. Krumbhaar.[33g] Footnote 116 *f* to *h* and *l*. Bishop, I. F., Jr.: Transient, Recurrent, Complete Left Bundle Branch Block, Am. Heart J. **15**:354, 1938.

129. (*a*) Kalett, J.: Bundle Branch Block, with Spontaneous Remission After 4 Years: Report of a Case, Am. Heart J. **29**:120, 1945. (*b*) Segers, M.; Lequime, J., and Denolin, H.: Rémission progressive d'un bloc de branche, Acta cardiol **2**:64, 1947.

130. (*a*) Kurtz.[64a] (*b*) Jones and Feil.[65] (*c*) Wolferth and Livezey.[67c] (*d*) Miller, R., and Perelman, J. S.: Multiple Disturbances of Rhythm and Conduction and Unusual Auricular T Wave in a Case of Myocardial Infarction, Am. Heart J. **31**:501, 1946. (*e*) Sodeman, W. A.; Johnston, F. D., and Wilson, F. N.: The Q_3 Deflection of the Electrocardiogram in Bundle Branch Block and Axis Deviation, ibid. **28**:271, 1944.

131. Carter, E. P., and Dieuaide, F. R.: Unstable Conduction in the A-V Bundle, Bull. Johns Hopkins Hosp. **34**:401, 1923.

132. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, Heart **8**:229, 1921.

mere delay in conduction in one branch can elicit a pattern of bundle branch block.[64b] However, it has been said that specific muscle conduction is auxomerous, i. e., the excitation wave can be normally conducted as long as one fiber remains intact.[133] This may account for the frequency of extensive bundle branch lesions observed at necropsy without the presence of intraventricular block in the electrocardiogram.

BILATERAL BUNDLE BRANCH BLOCK AND RELATION OF INTRAVENTRICULAR TO AURICULOVENTRICULAR BLOCK

The theoretically expected complete auriculoventricular block following interruption of both bundle branches is not always observed.[134] Rothberger and Winterberg [2b] cut the left bundle branch of the canine heart and the pattern of left bundle branch block appeared, regardless of whether the right bundle branch had been previously severed or not. When complete interruption of one bundle branch was followed by temporary damage of the other branch,[135] various degrees of auriculoventricular block were seen without change of the pattern produced by the initial unilateral lesion. In a prevalent number of clinical cases exhibiting the known patterns of bundle branch block without auriculoventricular block, bilateral lesions of the bundle branches were seen on histologic examination of the conduction system.[136] Mahaim and his co-workers [137] recently reported a case in which they saw complete blocking lesions at necropsy in both bundle branches with only the pattern of left bundle branch block present in the electrocardiogram and without any changes which could be attributed either to the involvement of the right branch or to an auriculoventricular conduction disturbance. They called this "missed bilateral block." Yater,[75] on the other hand, reported an absence of lesions in the auriculoventricular node and common bundle in 3 cases of complete auriculoventricular block, but extensive bilateral lesions of the bundle branches were observed. He concluded that the usual cause of complete auriculoventricular block is bilateral bundle branch block. Instances of auriculoventricular block with QRS complexes of normal duration were attributed by him either to a single pacemaker in the intraventricular septum or to bilateral idioventricular pacemakers located below the areas of block and discharging simultaneously.

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133. Hansen, A. T.: On Intraventricular Conduction Disturbances in the Specific Conduction System of the Heart, Acta med. Scandinav. **117**:104, 1944.

134. Mahaim,[22] Yater and others.[75]

135. Scherf, A., and Shookhoff, C.: Reizleitungsstoerungen im Buendel, Wien. Arch. f. inn. Med. **11**:425, 1925.

136. Mahaim,[22] Yater.[76a]

137. Mahaim, I.; Winston, M. R., and Roesler, H.: Bilateral Missed Block, Am. Heart J. **25**:251, 1943.

The same controversy, viz., a single pacemaker with variable intraventricular conduction versus the presence of multiple pacemakers, is evident in the many attempts to explain the occurrence of QRS complexes of varying contour during complete auriculoventricular block. Such variability was first described by Mathewson [138] and has since been frequently noted. In a case cited by Cohn [139] the pattern of left bundle branch block alternated with that of right bundle branch block, while an auriculoventricular block progressed from partial to complete. He suggested that this was due to alternately depressed conduction in the bundle branches. Robinson,[88] Carter and Dieuaide [131] and others also stated the view that changes in intraventricular conduction accounted for such variability of the ventricular complexes, although a wandering pacemaker could not be ruled out.[88] The assumption of a shifting pacemaker has been based on experimental data of Wilson and Herrmann [132] by Don and associates [140] and on the long-continued constancy of the form of the aberrant conduction by Carter and McEachern.[116j] The presence of two ventricular pacemakers "with change in the leadership from one side to the other" was postulated by Gilchrist and Cohn.[141] Bain [142] analyzed four such tracings and came to the compromising conclusion that varying ventricular complexes of the bundle branch block type and with complete auriculoventricular heart block usually signify the presence of bilateral defects of conduction through the bundle branches. The impulse may arise from multiple sites in the ventricles; however, a single pacemaker is more likely in the absence of variations of the ventricular rate and of transitional ventricular complexes.

Variations in contour of QRS complexes from patterns of left to right bundle branch block, and with intermittent normal complexes apparently indicating normal intraventricular conduction, may also be observed in connection with first and second degree auriculoventricular block. Katz and associates [127d] described such changes in a case with Wenckebach periods. Dressler [143] presented 2 cases in which the

138. Mathewson, G. D.: Lesions of the Branches of the A-V Bundle, Heart **4**:385, 1913.

139. Cohn, A. E.: A Case of Transient Complete A-V Dissociation Showing Constantly Varying Ventricular Complexes, Heart **5**:5, 1913.

140. Don, C. S. D.; Grant, R. T., and Camp, P. D.: A Case of Complete Heart Block with Varying Ventricular Complexes, Heart **16**:145, 1932.

141. Gilchrist, A. R., and Cohn, A. E.: Varying Ventricular Complexes in Complete Heart Block, Am. Heart J. **3**:146, 1928.

142. Bain, C. W. C.: Variable Ventricular Complexes in Heart Block and Their Relation to Bilateral Bundle Branch Block, Brit. Heart J. **3**:75, 1941.

143. Dressler, W.: Delayed Conduction in the Bundle Branches: A Report of 2 Cases in Which the P-R Interval Increased with Changes from Left to Right Bundle Branch Block, Am. Heart J. **29**:728, 1945.

change of left to right bundle branch block occurred without dropped beats but with variations in the P-R interval. Strauss and Langendorf [144] pointed out that, in a tracing exhibiting partial auriculoventricular block and QRS complexes of more than 0.12 second's duration, it may not be possible to determine the presence of (*a*) bilateral partial bundle branch block, (*b*) complete block of impulse transmission in one bundle branch plus partial block in the other or (*c*) unilateral involvement of branches (partial or complete) plus additional involvement in the common bundle or in the auriculoventricular node. Bilateral partial bundle branch block with an equal delay on the two sides may produce simple auriculoventricular block without prolongation of QRS complexes. In the case presented by the authors, the common type of block was seen, with a slow ventricular rate due to periods of 2:1 and 3:1 auriculoventricular block; the uncommon type of block was seen during 1:1 conduction, and the explanation suggested was the presence of partial block in the two main bundle branches, with a shorter relative refractory phase in that bundle branch which had the longer absolute refractory phase. A similar case was reported by Miller and Perelman,[180d] in which different types of conduction disturbance and arrhythmias were present after myocardial infarction. Left bundle branch block was present when the auriculoventricular block was complete and right bundle branch block when there was no auriculoventricular block. Differences in the refractory period of the two bundles were also assumed by Burchell [145] as the explanation of varying contours of ventricular captures in a case with dissociation.

ANATOMY OF CONDUCTION SYSTEM

We shall attempt to review only a few pertinent studies of the anatomy of the conduction system. The early studies dealt with the gross and microscopic anatomy of the nodes, the auriculoventricular bundle and its two main branches and the terminal subendocardial Purkinje network. The early view that the conduction system could be easily seen grossly was dispelled by the studies of Mahaim,[22] in which he pointed out that the conduction system could usually be observed only microscopically with careful serial sections. The studies of Lewis and Rothschild [88] led to the widespread belief that the excitation wave traveled rapidly throughout the subendocardial system, then spread through the ordinary ventricular muscle at right angles to the direction

144. Strauss, S., and Langendorf, R.: Bilateral Partial Bundle Branch Block, Am. J. M. Sc. **205**:233, 1943.

145. Burchell, H. B.: Sino-Auricular Block, Interference Dissociation, and Different Recovery Rates of Excitation in the Bundle Branches, Brit. Heart J. **11**:230, 1949.

of the fibers at a much slower rate. There is general agreement that the posterobasal left ventricle and the conus arteriosus are the last portions of the myocardium to be activated.[146]

The Glomsets[147] were unable to find any part of the conduction system in the heart of ungulates, dogs or men, and they were of the opinion that the dissections described by others were of ordinary muscle tissue. They stated that there is no evidence to support the myogenic origin of cardiac activation, the latter being under nervous control obtained through the rich intrinsic nerve elements present in the heart.[148] They also wrote that the heart is not a syncytium but is composed of distinct muscle cells.[88] Robb and his collaborators[25] concurred for a time, pointing out, however, that any given muscle bundle is a syncytium with its own precise blood supply. With these few exceptions there is almost universal agreement concerning the existence of a specific, neomorphic, myogenic conduction system.[149] Furthermore, as Wilson and his associates pointed out:

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146. (*a*) Barker and others.[20] (*b*) Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, Arch. Int. Med. **72**:210 (Aug.) 1943. (*c*) Nahum, L. H., and Chernoff, H. M.: The Spread of Excitation and the Order of Repolarization in the Human Heart, Federation Proc. **8**:117, 1949.

147. Glomset and others.[88] Glomset, D. J., and Birge, R. F.: A Morphologic Study of the Cardiac Conduction System: IV. The Anatomy of the Upper Part of the Ventricular Septum in Man, Am. Heart J. **29**:526, 1945. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog and Man: II. The Purkinje System, ibid. **20**:677, 1940.

148. Stotler, W. A., and McMahon, R. A.: The Innervation and Structure of the Conduction System of the Human Heart, J. Comp. Neurol. **87**:57, 1947.

149. (*a*) Mahaim.[22] (*b*) Katz.[27d] (*c*) Cardwell, J. C., and Abramson, D. I.: The Atrioventricular Conduction System of the Beef Heart, Am. J. Anat. **49**:167, 1935. (*d*) Abramson, D. I., and Cardwell, J. C.: Proc. Am. Physiol. Soc. **46**:1, 1934. (*e*) Abramson, D. I., and Margolin, S.: A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricle, J. Anat. **70**:250, 1936. (*f*) Abramson, D. I., and Jochim, K. E.: The Spread of the Impulse in the Mammalian Ventricle, Am. J. Physiol. **120**:3, 1937. (*g*) Mahaim, I., and Winston, M. R.: Recherches d'anatomie comparée et de pathologie expérimentale sur les connexions hautes du faisceau de His-Tawara, Cardiologia **5**:189, 1941. (*h*) Davies, F.: The Conducting System of the Vertebrate Heart, Brit. Heart J. **4**:66, 1942. (*i*) Walls, E. W.: Dissection of the A-V Node and Bundle in the Human Heart, J. Anat. **79**:45, 1945. (*j*) Lev, M., and Killian, S. T.: Hypoplasia of the Aorta Without Transposition, with Electrocardiographic and Histopathologic Studies of the Conduction System, Am. Heart J. **24**:794, 1942. (*k*) Truex, R. C., and Copenhaver, W. M.: Histology of the Moderator Band in Man and Other Mammals with Special Reference to the Conduction System, Am. J. Anat. **80**:173, 1947. (*l*) Kistin, A. D.: Observations on the Anatomy of the Atrioventricular Bundle (Bundle of His) and the Question of Other Muscular Atrioventricular Connections in Normal Human Hearts, Am. Heart J. **37**:849, 1949.

The bundle branches may or may not exist as sharply differentiated muscular structures in the histologic sense, but they surely exist as distinct entities in the physiologic sense and play an important role in the transmission to the ventricular muscle of impulses that originate in the auricles.[150]

There was only an occasional suggestion prior to 1931 that specific conduction tissue actually could be seen in the ordinary muscle beyond the subendocardial arborizations. Whalin [151] observed a network of conduction fibers ramifying throughout the septum of the calf heart. Soon after, Cardwell and Abramson [149c] studied the conduction system in the beef heart and again observed a network of conduction fibers arising in the subendocardium which penetrated and ramified throughout the muscle of the septum and the free walls of both ventricles. They later confirmed these observations.[149d, e] Little attention has been given to these important investigations. Abramson and Jochim [149f] also studied the spread of the activating impulse in the dog heart under controlled conditions and confirmed the observations of Robb [152] that the impulse reached the epicardial surfaces of both ventricles almost simultaneously and at right angles to the direction of the ventricular muscle. Robb [152] offered further support for the existence of septal ramifications. The careful studies of Davies,[149h] Truex and Copenhaver [149k] and Rijlant [153] confirmed the existence of a conduction network ramifying throughout the ventricular muscle and in direct continuity with ordinary muscle fibers. The studies of Mahaim [154] further demonstrated that conduction tissue is connected with ordinary muscle high in the septum by delicate connections, predominantly on the left side, which unite the common bundle and one or both of the bundle branches with septal muscle. These high connections assure a direct conduction pathway between the upper septal muscle and conduction tissue in an area not directly communicating with the terminal Purkinje network [155] and may explain why auriculoventricular block is sometimes absent despite extensive bilateral histologic bundle branch lesions.[156] As has been stated, "The specialized cardiac conducting system of . . . homoiothermal

150. Wilson, F. N.; Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the ECG, in Dock, W., and Snapper, I.: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1947, vol. 2.

151. Whalin, B.: Upsala Läkaref. Förh. **34**:769, 1928, cited by Abramson and Margolin.[149e]

152. Robb, J. S.: Concerning the Distribution of the Purkinje Substance and Certain Physiological Implications Dependent Thereon, Am. J. Physiol. **116**: 129, 1936.

153. Rijlant, P.: La conduction dans le cœur du mammifère, Arch. internat. de physiol. **33**:325, 1931.

154. Mahaim.[22] Mahaim and others.[137] Mahaim and Winston.[149g]

155. Mahaim and Winston.[149g] Robb.[152]

156. Rothberger and Winterberg.[3b] Mahaim and others.[137]

vertebrates is not a remnant of more extensive tissues of similar structure in lower vertebrate hearts. It is a neomorphic development associated with the more rapid rate of the heart." [149h]

DERIVATION OF THE ELECTROCARDIOGRAPHIC PATTERN

Various mechanisms have been proposed to explain the pattern of intraventricular block. The concept of bundle branch block rests on the early experiments in which the bundle branches were severed in the dog's heart, with the production of characteristic changes in the electrocardiogram.[157] There has since been widespread acceptance of the view that the pattern of intraventricular block is almost invariably due to an organic blocking lesion or functional delay in the passage of the activating impulse through one of the main bundle branches. As was pointed out, the histologic evidence underlying this concept contains significant discrepancies.

Wilson and associates [84b] championed the mechanism of bundle branch block. The final QRS deflection in patterns of intraventricular block was described to the electromotive forces developed by septal activation from the contralateral to the blocked ventricle, combined with the forces developed by the spread through the free wall of the blocked ventricle. In right bundle branch block early narrow limb lead deflections were ascribed to forces developed by activation of the thick-walled left ventricle which overbalanced the oppositely directed septal forces. In left-sided block, the corresponding initial limb lead deflections were tiny or absent, since the forces developed by excitation of the thinner right ventricle were less than those which originated from the septal activation.[44] This mechanism, then, rested on the concept that the course of the impulse was normal in the unaffected ventricle; activation of the blocked ventricle was delayed because the stimulus was considered to traverse the ordinary muscle of the septum to reach the conduction tissue of the blocked side.[158] Atypical patterns and low voltages were ascribed to concomitant factors, such as myocardial infarction, fibrosis, hypertrophy or congestive failure.

On the other hand, septal activation, in the opinion of some, does not contribute to the main broadened deflection. Fenichel [21] expressed the view that the principal deflection represented only activation of the free wall of the blocked ventricle, septal effects being early and contributing only to initial deflections. Careful histologic and experimental studies [149c-g] demonstrated the existence of a rich septal network of specific conduction tissue which joins the endocardial surfaces of the

157. Rothberger and Winterberg.[2b] Lewis.[8b, c] Wilson and Herrmann.[12b]

158. Wilson, F. N.: The Form of the ECG, in Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease, Philadelphia. F. A. Davis Company, 1940, vol. 1.

septum and which permits rapid transseptal conduction in the presence of bundle branch block.[140f, h] However, intracavity electrodes in dog and man demonstrated activation of the septum in two phases in right bundle branch block.[40] It was shown that the normal early spread of the impulse from the left to the right side across the upper septum still occurs in right bundle branch block; transseptal activation again occurs below the site of block, making apparent the mechanism of the rsR′ complex observed in right-sided chest leads.[159] The initial R wave may be ascribed to the early left to right septal activation above the site of block; the late, tall R′ is recorded during the activation of the septum below the site of block (ascending limb) and the free wall of the right ventricle (final portion). In left bundle branch block, the normal early left to right transseptal conduction is usually prevented and the right ventricular cavity potential remains negative throughout the cycle, whereas an equiphasic RS complex was recorded in a lead obtained from the cavity of the left ventricle. Thus, a Q wave is ordinarily absent from leads reflecting left ventricular epicardial potentials and the small initial R wave usually seen in chest leads on the right side will often be absent. The final QRS deflection may again be ascribed to the late activation of the free wall of the left ventricle, the earlier deflections being due to transseptal conduction from the contralateral ventricle.[158] The left-sided precordial leads will, thus, have an M-shaped complex and the right-sided leads will display broad, deep S waves, sometimes preceded by a small R wave.

The concept of bundle branch block as the sole mechanism to account for patterns of intraventricular block has been challenged. A peripheral conduction defect is mentioned in most texts but is apparently little used clinically. The term "arborization block" was first given to atypical widened complexes with low voltage [9] and was ascribed to extensive fibrosis in subendocardial regions. It was further postulated that impulse transmission might be abnormal consequent to delay in the ventricular muscle.[42] Willius [11] suggested that such involvement could lead to a circuitous and aberrant path of impulse transmission through the free ventricular wall. Wilson, Johnston and their associates,[160] however, defined arborization block patterns as widened complexes without typical contours of bundle branch block and ascribed them to the general depression of conduction tissue which may occur with myocardial infarction, toxins or use of excessive amounts of quinidine.

Cardiomegaly has also been implicated in the development of intraventricular block. Fahr [16] noted the similarity of patterns of heart strain

159. Seligmann, A.; Steinberg, M. F.; Kroop, I. G., and Grishman, A.: Simultaneous Right and Left Sided Intracardiac Electrocardiography in Man: Right Bundle Branch Block, Bull. New York Acad. Med. **25**:443, 1949.

160. Wilson.[44] Wilson and others.[54b]

and intraventricular block and was led to conclude that both were due to actual increased length of the conduction system, the impulse having to traverse a longer course. Although it is difficult to conceive of such a mechanism, the possibility becomes greater with the realization that a mere delay in impulse transmission without actual blocking in one bundle branch can produce a pattern of intraventricular block.[182] Furthermore, conduction time normally is known to be longer in larger hearts, such as the elephant's.[83] Cases of prolonged heart strain have been observed to progress into patterns of intraventricular block[161] and these observations were offered in support of the mechanism of both being due to impaired conduction.[162] Cardiomegaly is often observed in patients with intraventricular block.[163] Furthermore, a definite correlation has been demonstrated between progressive ventricular enlargement and progressive evolution in the pattern from that of left ventricular hypertrophy to intraventricular block in patients with hypertensive vascular disease[161d] and aortic valvular disease.[161e] The QRS interval does widen with the development of hypertrophy contours,[161e] but it is the general opinion that ventricular strain alone rarely causes a QRS interval greater than 0.10 second.[164] Master and associates[163d] also studied patients with intraventricular block and noted enlargement of the ventricle in 94 per cent of 100 patients. They concurred with Fahr[16] and Rasmussen[165] that intraventricular block is related primarily to cardiac enlargement and diffuse myocardial damage, the predominant ventricular enlargement determining the site of block and the myocardial damage accounting for the defective conduction. It is well known that there is a close relation between prolonged ventricular hypertrophy and intraventricular block;

161. (*a*) Luten and Grove.[62] (*b*) Hyman and Parsonnet.[63] (*c*) Willius, F. A.: The Progression of Myocardial Disease as Recorded by Serial Electrocardiograms, M. Clin. North America **16**:1493, 1933. (*d*) Rasmussen, H., and Thingstad, R.: Cardiovascular Changes in Essential Hypertension with Special Reference to the Electrocardiogram in Hypertension, Acta med. Scandinav. **101**:237, 1939. (*e*) Rasmussen, H.: The Electrocardiogram in Aortic Insufficiency with Special Reference to the Development of the Left Bundle Branch Block Electrocardiogram, ibid. **118**:385, 1944.

162. (*a*) Luten and Grove.[62] (*b*) Rasmussen.[161e] (*c*) Glomset, D. J., and Birge, R. F.: A Morphologic Study of the Cardiac Conduction System: V. The Pathogenesis of Heart Block and Bundle Branch Block, Arch. Path. **45**:135 (Feb.) 1948.

163. (*a*) Graybiel and Sprague.[35] (*b*) Rasmussen and Thingstad.[161d] (*c*) Glomset and Birge.[162c] (*d*) Master, A. M.; Kalter, H.; Dack, S., and Jaffe, H. J.: The Relation Between Bundle Branch Block and Cardiac Enlargement, Am. Heart J. **20**:186, 1940.

164. East and Bain.[86b] Wilson.[158]

165. Rasmussen, H.: Experimental Production of Bundle Branch Block Electrocardiograms by Acute Dilatation of the Right and Left Heart, Acta med. Scandinav. **110**:32, 1942.

left-sided block is usually seen in patients with hypertensive vascular disease, aortic valvular lesions or coronary sclerosis and right-sided block in patients with rheumatic heart disease, cor pulmonale or congenital heart disease.[108] On the other hand, Wilson and associates [166] explained similarities in the patterns of strain and block by pointing out that in both conditions the free wall of the ventricle is activated in the same direction and that bundle branch block does not materially alter the direction of impulse spread except in the intraventricular septum. They further pointed out one significant difference: Leads reflecting left ventricular potentials commonly have initial Q waves in patterns of left ventricular hypertrophy and such waves are rare with left bundle branch block.[167]

It is clear from theoretic, experimental and intracavity lead studies that intraventricular block is usually due to an organic or functional block in one of the main bundle branches. Nevertheless, there has accumulated certain evidence to suggest a peripheral origin of delayed conduction in the subendocardium or free wall of the ventricles in some cases.

ELECTROCARDIOGRAPHIC PATTERN OF COMPLETE BUNDLE BRANCH BLOCK

Characteristic patterns of bundle branch block may be altered by associated myocardial fibrosis, hypertrophy and infarction and, particularly, by variations in the "electrical" positions usually encountered.[44] Diagnosis should be made from precordial lead patterns, which vary little even with unusual rotations [56]; leads V_1 and V_5 (or V_6) are most suitable in this regard. In left bundle branch block, lead I usually displays a monophasic, widened, notched and slurred, flat-topped or bifid R wave (common type); the T wave is large and inverted, and the S-T segment is usually depressed. The pattern is similar in other leads reflecting left ventricular potentials, such as V_5, V_6 and aV_L. Lead I almost invariably displays a diphasic or triphasic complex in right bundle branch block; there may be a small Q wave, a narrow R wave—which may be small (uncommon type) or tall (S type)—and a broad, slurred S wave. The T wave is usually upright. The pattern in leads II and III, as well as in lead I, depends materially on "electrical" position. Illustrative cases will be presented elsewhere [7]; no attempt will be made to reproduce these patterns in this review.

The precordial leads usually have characteristic similar patterns in all electrical positions. The transition zone in serial leads is found near position C_1 in right bundle branch block and near C_5 in left bundle branch block; thus, the characteristic patterns may not be observed unless one records leads V_1 and V_6.[24a] In right bundle branch block, a wide, slurred S wave is seen in leads reflecting left ventricular potentials and is pre-

166. Wilson and others.[22a] Wilson.[158]
167. Wilson.[158] Sodeman and others.[180e]

ceded by a slender R wave and occasionally a small Q wave; leads reflecting right ventricular potentials display an M-shaped rsR′ complex or occasionally a qR or only an R wave which is notched and slurred or flat topped. In left bundle branch block leads over the right ventricle consist of a wide, slurred inverted complex with or without a small initial R wave; leads reflecting left ventricular potentials display an M-shaped bifid R wave which occasionally may be only a slurred or flat-topped R wave. It has long been realized that the time of onset of the "intrinsicoid" deflection in left-sided precordial leads (V_5, V_6), compared with that in right-sided leads (V_1), will best indicate whether the conduction delay is localized in the right or left side of the heart[168]; this is most easily determined by simultaneously recording left-sided and right-sided precordial leads.[169]

The pattern inscribed in the aV limb leads also necessarily depends on the "electrical" position and may fail to resemble any of the recorded precordial leads, since similar potential variations may not be simultaneously present over the respective ventricular surfaces.[170] Thus, in right bundle branch block it is rare for ventricular complexes of leads aV_L or aV_F to resemble closely lead V_1, and the aV lead having a broad S wave has a much smaller R wave relative to its height than the precordial leads.[158]

S-T segments are depressed or elevated in a direction opposite to the final QRS deflection; T waves are usually large and oppositely directed from the broadened QRS deflection [37d] but not invariably.[39] The relation between QRS and T waves was studied,[171] and it was shown that the T wave contour and direction could be predicted from the QRS pattern, as in instances of normal intraventricular conduction. Atypical T waves do not necessarily indicate anything more than uncomplicated intraventricular block.

Amplitudes of QRS and T waves in intraventricular block are often large, probably because of the late and unopposed activation of the free wall of the blocked ventricle.[172] When right-sided block is associated with right ventricular hypertrophy, the late R waves in right-sided precordial leads are tall and left-sided chest leads record smaller R waves

168. Wilson and others.[23b] Wilson and others.[24a] Wilson.[44]

169. Holzmann, M.: Klinische Elektrokardiographie, Zurich, Fretz & Wachsmuth, 1945.

170. Wilson and associates.[54b] Wilson, F. N.; Johnston, F. D.; Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surfaces and the Form of the Ventricular Electrocardiogram in Leads from the Precordium and the Extremities, Tr. A. Am. Physicians **56**:258, 1941.

171. Sodeman, W. A.: A Study of the T Wave of the Electrocardiogram in Left Bundle Branch Block, J. Clin. Investigation **19**:784, 1940.

172. Wilson and Hermann.[12b] Wilson. [158]

and deeper S waves than are usually observed. When right bundle branch block is associated with left ventricular hypertrophy, the latter may be suspected with the appearance of excessively tall R waves and T wave inversions in precordial leads reflecting left ventricular potentials.[173] Prominent notching and slurring are usually present and have been ascribed to the irregular growth and decline of manifest potential differences, to associated myocardial damage and to superimposition of levocardiograms and dextrocardiograms.[174] The presence of low voltages [9] does not necessarily obviate the diagnosis of uncomplicated bundle branch block,[175] although often signifying superimposed defective intraventricular conduction. Deep apical notching producing bifid complexes is ascribed to the time interval separating activation of right and left ventricles.

The presence of a Q wave in leads reflecting left ventricular potentials in left bundle branch block has been a matter of concern and is noted only rarely in uncomplicated left bundle branch block.[130e] Such Q waves are commonly present in experimental left bundle branch block in dogs,[132] owing to the "electrical" position of the canine heart.[52b] The absence of a Q wave in lead I and left precordial leads in human left bundle branch block was stated to be due to the late onset of left ventricular forces. The disappearance of these Q waves in records which progressed from left ventricular hypertrophy to left bundle branch block was offered as evidence of the different etiologic mechanism involved in such cases.[176] However, it is now realized that the absence of the initial negativity in leads reflecting left ventricular potentials is due rather to the absence of early left to right transseptal transmission of impulses. The presence of Q waves in leads I, aV_L and V_5 or V_6 in left bundle branch block (horizontal position) frequently indicates anteroseptal myocardial infarction which permits the initial negativity of the right ventricular cavity to be transmitted to these leads.[177] Such Q waves occasionally occur in the absence of infarction of the septum and have been ascribed to initial positivity of the right ventricular epicardial surface,[130e] peculiarities of the conduction system and an "electrically" vertical position and thus, may be produced by deep inspiration.[178] However, even in typical "electrical"

173. Barker, J. M., and Valencia, F.: The Precordial Electrocardiogram in Incomplete Right Bundle Branch Block, Am. Heart J. **38**:376, 1949.

174. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, Paul B. Hoeber, Inc., 1941. Wilson and Herrmann.[12b]

175. Carter.[10] Yater.[76b]

176. Wilson and others.[54b] Sodeman and others.[130e]

177. Langley and others.[85b] Sodeman and others.[130e]

178. Lapin, A. W., and Sprague, H. B.: Respiratory Movements as a Factor in the Production of Q Waves in Lead I and in Unipolar Leads from the Left Precordium in Human Left Bundle Branch Block, Am. Heart J. **25**:962, 1948.

positions, if the block in the bundle branch is low enough in the septum, the normal initial left to right septal conduction might still be present to account for the appearance of such Q waves.

INCOMPLETE BUNDLE BRANCH BLOCK

The concept of incomplete bundle branch block rests on the experiments in which it was noted that a delay in conduction through a bundle branch not great enough to inscribe a pattern of complete block would produce complexes transitional in form and duration between the latter and normal tracings.[179] These transitional complexes were also observed in records with intermittent intraventricular block[180] and in records observed to progress from a pattern of heart strain to that of bundle branch block.[181] The term incomplete bundle branch block has been improperly used in describing instances of 2:1 intraventricular block, more correctly designated as partial intraventricular block. Incomplete bundle branch block should not be used to describe records in which the contour of left and right bundle branch block is noted in alternating beats,[143] although such a pattern may be experimentally produced by unilateral bundle branch block, with a partial delay in the other bundle branch.[135] The term incomplete bundle branch block should be reserved for patterns closly resembling the contours of complete block but having a QRS duration of less than 0.12 second.[44] In incomplete right bundle branch block, the QRS duration may measure as little as 0.08 second.[173] Right-sided chest leads in incomplete right bundle block consist of a widened rSr′ complex in which the R′ is usually small or "embryonic" but may be large.[182] There is usually a slurred, prominent S wave in lead I and in left-sided chest leads.[54b] The difficulties involved in distinguishing certain patterns of ventricular hypertrophy from those of incomplete bundle branch block have been pointed out.[183] This difficulty is particularly acute in cases of patterns of left ventricular strain in which the QRS interval is widened.[173] The absence of a Q wave in left ventricular leads is not a differential factor, although its presence tends to rule out a conduction defect in a bundle branch.[130e] Differentiation of high grade incomplete and complete right bundle branch block may be impossible, particularly when the incomplete block is associated with right ventricular hypertrophy.[173]

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179. Rothberger and Winterberg.[2b] Wilson and Herrmann.[12b] Stenström.[13] Wilson and Herrmann.[132]

180. Segers and others.[129b] Barker and Valencia.[173] Scherf, D., and Boyd, L. J.: Clinical Electrocardiography, London, W. Heinemann, Ltd., 1940.

181. Luten and Grove.[62] Hyman and Parsonnet.[63] Footnote 161 *c* to *e*.

182. Wilson and others.[54b] Barker and Valencia.[173]

183. Wilson and others.[54b] Wilson, F. N.: The Clinical Value of Chest Leads, Brit. Heart J. **10**:88, 1948.

The pattern of incomplete block is derived as a fusion effect in which the blocked ventricle is activated both from the contralateral bundle branch through the septum and from above, the impulse merely being retarded and not interrupted in its passage down the homolateral bundle branch.[86a] Such fusion patterns may be seen in lower degrees of aberrancy in ventricular responses to auricular premature beats.[184] Further difficulties occur in distinguishing patterns of incomplete block from those of defective conduction in the free walls of the ventricles; thus, the term defective intraventricular conduction has been used to include both.[87] Bain [184] described three types of incomplete bundle branch blocks. Type 1 has a QRS duration which is widened, but measures less than 0.10 second, and there is no axis shift. It is ascribed to a bilateral delay in the main bundle branches such as can occur with auricular premature beats and aberrant ventricular response. Type 2 occurs with a partial delay down one bundle branch and resembles the pattern of complete bundle branch block, with a QRS interval less than 0.10 second; type 3 refers to transitional complexes due to bilateral bundle branch delay but with a greater delay in one of the branches. The pattern of bundle branch block with a QRS duration of less than 0.10 second will be observed with alternating patterns of left-sided and right-sided block.

EXPERIMENTAL AND CLINICAL STUDIES ON A PERIPHERAL VENTRICULAR ORIGIN OF INTRAVENTRICULAR BLOCK

Typical patterns of intraventricular block can be produced experimentally by blocking conduction in either main bundle branch. The concept of intraventricular block due to conduction delays distal to the main bundle branches has received relatively little attention since the term arborization block was first used to describe such a mechanism.[9] Recently however, such patterns have been observed experimentally following the production of myocardial congestion due to ligation of the coronary sinus.[185] On the other hand, subendocardial fibrosis produced by ligation of the coronary artery,[12a] section of subdivisions of the main bundle branches [12b] and extensive subendocardial scarification [186] failed to produce widening of QRS intervals. Nevertheless, the form of the QRS complexes was altered during these studies, indicating a disturbed order of activation due to a delay in the areas involved. Activation of these areas was completed by the time excitation ended at the basal

184. Bain, C. W. C.: Incomplete Bundle Branch Block, Brit. Heart J. **6**:139, 1944.

185. Unghvary, L.: Pathogenesis of Arborization Block in the Electrocardiogram, Orvosi hetil. **89**:373, 1948.

186. (*a*) Rosenthal.[74] (*b*) Pruitt, R. D.; Barnes, A. R., and Essex, H. E.: Electrocardiographic Changes Associated with Lesions in the Deeper Layers of the Myocardium, Am. J. M. Sc. **210**:100, 1945.

portions of the left ventricle, so that the QRS duration was not increased. Furthermore, in 2 dogs in which subendocardial scarification was extensive, widening of the QRS interval did occur.[186b] Significant QRS slurring, particularly apical notching in precordial leads outside the transition zone, may reflect small peripheral ventricular areas in which there is a delayed impulse conduction due to fibrosis. It is conceivable that such fibrosis, if extensive enough, could widen the QRS duration to 0.12 second or more and produce conspicuous slurring and notching [187]; low voltage would be also expected in such circumstances.[9] Significant slurring and apical notching of QRS waves in all leads are rarely seen in the absence of myocardial damage.[188]

Certain experimental studies have also implicated acute ventricular dilatation and strain in the mechanism of intraventricular block patterns. Acute dilatation of the right ventricle, such as occurs with acute cor pulmonale, is often early associated with a pattern of right intraventricular block, [82b] and hypoxemia was not observed to be the responsible factor.[120f] Acute ventricular dilatation and strain were produced by clamping the aorta and pulmonary artery, eliciting patterns of intraventricular block.[189] Studies of chronic heart strain and ventricular enlargement and their relationship to patterns of intraventricular block have already been discussed.[190] Different mechanisms were suggested to explain the association of intraventricular block with cardiac dilatation and strain. One such involves a delay in conduction consequent to a mechanical lengthening of the conduction system, causing a longer conduction pathway.[191] Gubner and Ungerleider,[192] however, called attention to the intramyocardial pressure gradient across the free wall of the ventricle. During part of systole, a great increase in intramyocardial pressure occurs in the deeper layers of the left ventricle wall, which exceeds the aortic pressure and obstructs coronary blood flow. The pressure developed in the auricles, right ventricle and subepicardial areas of

187. Pruitt and others.[186b] Pardee.[174] Burch, G. E., and Winsor, T.: A Primer of Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1949.

188. Reeser and others.[87b] Wedd, A. M.: The Clinical Significance of Slight Notching of the R-Wave of the Electro-Cardiogram, Arch. Int. Med. **23**:515 (April) 1919.

189. Rasmussen.[165] Robb, J. S., and Robb, R. C.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained: II. Left Ventricular Strain, Am. J. M. Sc. **203**:634, 1942.

190. Luisada.[103] Footnote 161 *c* to *e*. Master and others.[163d]

191. Fahr.[16] Rasmussen.[165]

192. Gubner, R., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy: Factors Determining the Evolution of the Electrocardiographic Patterns in Hypertrophy and Bundle Branch Block, Arch. Int. Med. **72**:196 (Aug.) 1943.

the left ventricle is not sufficient normally to interfere with blood flow in these areas. In the presence of increased intraventricular pressure the time at which the subendocardial regions receive no blood flow begins earlier and persists over a longer period. The ischemic subendocardial region might delay impulse conduction accordingly. In harmony with this is the well known site of predilection of myocardial fibrosis for the subendocardial regions of the left ventricle in patients with coronary insufficiency. Despite the evidence presented, it can be said that an intraventricular block pattern occurring in the presence of acute or chronic ventricular dilatation and strain might still be due to a bundle branch block delay rather than to one in the ventricular periphery. It was shown [193] that pressure by an intracardiac catheter on the septum could produce a transient right bundle branch block.

The term focal block originally was applied to a delay in activation of a small circumscript area in the free wall of the ventricle, of a magnitude sufficient to inscribe a widened complex and a late "intrinsicoid" deflection confined to certain leads in close proximity to that area. Thus, the pattern of intraventricular block would appear only in one or two precordial leads and might be absent in the limb leads, particularly with a focal block of the right ventricle.[54b] Two instances of focal right intraventricular block were first reported by Weinberg and Katz,[194] but little recognition has been subsequently given to such a concept. The precordial distribution of these widened, M-shaped complexes was limited to small areas, indicating a region of delay so small that the magnitude of the electrical field created by it was also small.[67d] Since the widened rSr′ pattern is limited to one or two precordial leads, this pattern may be distinguished from incomplete right bundle branch block [132] and from the normal rSr′ contour which may occasionally occur normally in a lead recorded over the conus arteriosus.[195] Recently, Kert and Hoobler [193] were able to produce a similar focal delay in conduction by pressing the tip of an intracardiac catheter against the right ventricular endocardium.

Segers [196] noted that the contour of the initial portions of the QRS complex remained unchanged in cases of intermittent block of the S type, an observation previously emphasized.[67c] He concluded that the S type block must represent a peripheral ventricular delay in conduction and not a bundle branch block. Vector studies have been claimed to substantiate the peripheral origin of block in the S type pattern located

193. Kert, M. J., and Hoobler, S. W.: Observations on the Potential Variations of the Cavities of the Right Side of the Human Heart, Am. Heart J. **38**:97, 1949.

194. Weinberg, H. B., and Katz, L. N.: Two Unusual Types of Electrocardiograms, Am. Heart J. **19**:519, 1940.

195. Wilson and others.[22a] Wilson and others.[54b] Gardberg and Ashman. [146b]

196. Segers, M.: Le bloc focal, Cardiologia **3**:136, 1948.

in either the right ventricle [196] or the left ventricle [197] and have further demonstrated a bundle branch block mechanism in the common and uncommon types of block.[198]

Holzmann [169] used the term arborization block also to designate intraventricular block which is due to a delay in the free wall of the ventricle. In the left ventricle he recognized an "anterior" type which produces pronounced QRS slurring and notching in precordial leads, a pattern resembling left bundle branch block in the limb leads, with only slight delay in the time of onset of the "intrinsicoid" deflection; he further recognized a "posterocaudal" type in which the QRS interval is prolonged, without a delay in the "intrinsicoid" deflection, and in which there is definite slurring and notching in the final portions of the QRS complex but with normal initial phases.

Segers [199] recently expanded the concept of peripheral types of defective conduction, based partly on the experimental work of Rijlant.[153] He assumed correctly that Purkinje tissue ramifies throughout the free wall of the ventricle and is in direct continuity with ordinary muscle; a partial delay or complete block of impulse transmission could occur at the junction between specific and ordinary muscle. A new terminology is introduced in this regard. A "major" block is indicated by a QRS interval greater than 0.12 second and a "minor" block by an interval less than 0.12 second. "Parietal" block refers to defective conduction throughout the entire thickness of the ventricular wall and causes slurring throughout the QRS complex; a "subepicardial" conduction defect will elicit slurring only in the final QRS deflections. If the free wall of the entire ventricle is involved, the term "global" block is used, and, if the defect is limited to only a portion of the free wall, the term "focal" block is used. The S type block is considered to be a "major, focal, subepicardial" block in the right ventricle. A "focal, minor" right-sided block gives the pattern previously described by Weinberg and Katz [194] as focal block. The uncommon type is stated to be a bundle branch block of the right side and the common type to be a bundle branch block of the left side, when there are large voltages with bifid, M-shaped complexes in leads reflecting left ventricular potentials. A "focal left" ventricular block is shown

197. Meyer, P., and Schmidt, C.: Étude électrocardiographique de blocs localisés dans certaines régions du ventricule gauche (blocs focaux) en particulier de syndromes représentant l'homologue du bloc de Wilson pour le ventricule gauche, Arch. d. mal. du cœur **41**:707, 1948.

198. Vastesaeger, M. M.: Les troubles de la conduction intraventriculaire chez l'homme, Acta cardiol., 1946, supp. 1, p. 1. Cabrera, E.: Bases électrophysiologiques de l'électrocardiographie: Applications cliniques, Paris, Masson & Cie, 1948.

199. Segers, M.: Nouvelles bases d'interprétation de l'électrocardiogramme normal et pathologique, Acta cardiol, 1948, supp. 4, p. 1; The Different Types of Intraventricular Block, Am. Heart J. **37**:92, 1949.

by a widened complex, as in the common type, in which, however, the R waves are peaked and are slurred only on the downstroke; the widened complexes will be noted only in leads directly over the blocked area. A "major focal" left block would have similar complexes in all leads, a QRS interval greater than 0.12 second and an "intrinsicoid" deflection delay greater than 0.05 second. When the QRS duration is less than 0.12 second, when the onset time of the "intrinsicoid" deflection is less than 0.05 second and when the widened complexes are limited to several leads over a small precordial area, it is termed a "minor focal" left block. Incomplete bundle branch block, in his opinion, will have a slurred upstroke and slow ascent of the R waves, with a delay in the onset of the "intrinsicoid" deflection of less than 0.05 second but will be noted in all leads.

How much of this classification will be substantiated, only time can tell. However, Segers' work has tended to stress the view that many parts of the conduction system may be involved in intraventricular block and that the term bundle branch block may be too restricted a concept.

SUMMARY

A review of the existing literature dealing with defective intraventricular conduction is presented. The initial confusion concerning the localization, the clinical significance and the prognosis of intraventricular conduction disturbances is largely resolved. The term intraventricular block seems more appropriate than the term bundle branch block, since intraventricular block includes the latter, as well as defective impulse transmission in the free walls of the ventricles.

PRIMARY HODGKIN'S DISEASE OF THE LUNG

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THE INCIDENCE of pulmonary involvement in Hodgkin's disease varies in percentage among different communities and clinics. Falconer and Leonard [1] reviewed the literature to 1936, and their tabulation of 125 cases of Hodgkin's disease collected from various reports in this country and abroad showed pulmonary involvement in 47 cases, 37.6 per cent of the total. Of 29 cases of Hodgkin's disease studied by these authors, 9 revealed clinical or pathologic evidence of pulmonary involvement.

PATHOLOGIC ASPECTS

In many reports of cases of pulmonary Hodgkin's disease that were reviewed, definite proof was given of the primary or secondary nature of the lesion; however, one can easily come to the conclusion that a large majority are of the secondary type.[2] It is evident that the primary type is rare, although Moolten [3] in his most extensive review of the subject stated that the incidence of the primary type is as high as 10 per cent. The probable source of Hodgkin's disease is the lymph nodules in the parenchyma of the lung and the submucosa of the bronchi. The commonest source of the secondary type of pulmonary Hodgkin's disease is invasion from the mediastinal lymph nodes. Other authorities included dissemination of the lesion from the primary focus

From the Department of Pathology, Montefiore Hospital.

1. Falconer, E. H., and Leonard, M. E.: Hodgkin's Disease of the Lung, Am. J. M. Sc. **191**:780, 1936.

2. (*a*) Bernard, J.: Les formes pleuro-pulmonaires primitives de la maladie de Hodgkin, Prat. méd. franç. **13**:286, 1932. (*b*) Schaefer, A., and Wurm, H.: Lymphogranulom der Lungen mit Kavernenbildung, Fortschr. a. d. Geb. d. Röntgenstrahlen **47**:254, 1933. (*c*) Weber, H.: Lungenlymphogranulome, Beitr. z. path. Anat. u. z. allg. Path. **84**:1, 1930. (*d*) Lenk, R.: Die Lymphogranulomatosa der Lunge, in Holzknecht, G.: Handbuch der theoretischen und klinischen Röntgenkunde, Vienna, Julius Springer, 1929, vol. 1, p. 196. (*e*) Whitaker, L. R.: Malignant Lymphoma (Hodgkin's Disease): A Radiographic Study, Arch. Int. Med. **32**:538 (Oct.) 1923.

3. Moolten, S. E.: Hodgkin's Disease of the Lungs, Am. J. Cancer **21**:253, 1934.

in the spine, pericardium, pleura or thymus.[4] On further infiltration the parenchyma of the lung is most likely involved by invasion of pulmonary vessels or lymph channels, with infiltration even of the alveoli. According to Versé's [5] classification of pulmonary Hodgkin's disease, there are five types of gross pathologic invasion: (1) hilar node involvement with direct invasion of pulmonary tissue; (2) hilar node involvement with intrabronchial and peribronchial spread into the lungs; (3) lobar infiltration with bronchomediastinal involvement; (4) confluent lobular foci with associated involvement of lymph nodes, and (5) miliary disseminations.

The lesion on gross examination may simulate various pathologic conditions, such as unresolved lobar pneumonia, bronchopneumonia, disseminated tuberculosis and sarcoidosis. There are cases on record of definite cavity formation. Histologically, one can easily rule out the aforementioned conditions. The typical pleomorphism of cells, the presence of single and multinucleated giant cells (Sternberg-Reed cells), reticulum cells and eosinophils and the fibroblastic changes are the necessary criteria for the histologic diagnosis of Hodgkin's disease. The cells are more compact in the submucosal layer of the bronchi. They are more discrete surrounding the alveoli. There are always secondary changes in the lung, such as massive collapse, secondary infection with abscess formation, pneumonic consolidation and even bronchiectasis.

The clinical course and roentgenologic findings are most helpful in the absence of biopsy of lymph nodes. A pulmonary lesion followed by means of periodic roentgenologic study will often reveal its true nature on expansion of the lesion. Furthermore, radiosensitivity is one of the most important points of differentiation from other types of primary or secondary neoplasms of the lungs. Roentgen irradiation in this type of Hodgkin's disease brings about invariable improvement of the condition of the patient, with diminution or complete disappearance of the lesion; however, the lesion may return within several weeks or months. Clinically, an irregular fever of unknown origin that is difficult to explain in spite of minimal lesions in the lungs is quite significant. Afebrile intervals are sometimes seen. In the early phase

4. Wessler, H., and Greene, G. M.: Intrathoracic Hodgkin's Disease: Its Roentgen Diagnosis, J. A. M. A. **74**:445 (Feb. 14) 1920. Simonds, J. P.: Hodgkin's Disease, Arch. Path. **1**:394 (March) 1926. Lemon, W. S., and Doyle, J. B.: Clinical Observations on Hodgkin's Disease with Special Reference to Mediastinal Involvements, Am. J. M. Sc. **162**:516, 1923. Wallhauser, A.: Hodgkin's Disease, Arch. Path. **16**:522 (Oct.) 1933. Longcope, W. T., and McAlpin, K. R.: Hodgkin's Disease, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, chap. 1, pp. 4 to 12.

5. Versé, M.: Die Lymphogranulomatose der Lunge und des Brustfells, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 280.

of the disease anemia is not so prominent; but subsequently anemia may be one of the important observations. Loss of weight, although not consistent, does occur in a large majority. A loss of 10 to 50 pounds (4.5 to 22.7 Kg.) is common. The illness may be of the acute fulminating type in which death takes place within a matter of weeks or months, of the subacute or recurrent types which last months or years or of the chronic type which may last as long as fifteen to twenty years with remissions.

We do not intend to discuss or review cases of the secondary type of pulmonary Hodgkin's disease or those of doubtful origin. We are principally interested in cases that are primary in the lungs, proved on postmortem observation rather than on roentgenogram or by the clinical course. Such proved cases of primary pulmonary Hodgkin's disease are extremely rare. At times, it is almost impossible to establish the diagnosis of primary pulmonary Hodgkin's disease. There are limitations to both clinical and postmortem studies.

REPORT OF A CASE.

First Admission.—The patient, a 52 year old white male office clerk, was first admitted to the hospital on Dec. 6, 1948, to the service of Dr. Lawrence Wechsler. His chief complaints on admission were malaise, weakness and sore throat. He had been perfectly well until two weeks previously, with the exception of six "blackouts" during the past six to seven years. The typical episode lasted two to four minutes without convulsion or sequelae. The patient had been given diphenylhydantoin (dilantin®) sodium therapy for some time before his admission.

Subsequent Findings: During his stay in the hospital, the patient had petit-mal–like seizures. One patch of exudate was noted in the fundus of the left eye. The liver was palpable 2 fingerbreadths below the costal margin and was nontender. A diffuse nonpruritic erythematous rash was present on the abdomen, back and legs. A biopsy specimen was taken of a left axillary lymph node and the diagnosis of chronic toxic lymphadenitis with fibrosis was made.

Laboratory Data: Urinalyses showed persistent albuminuria. The leukocyte count ranged from 6,000 to 11,000 cells, with normal differential distribution. Anemia was slowly progressive, from 4,200,000 red blood cells per cubic millimeter and 12.5 Gm. of hemoglobin per hundred cubic centimeters to 3,400,000 red blood cells and 10.5 Gm. of hemoglobin. The test for Bence Jones protein gave negative reactions on two occasions. The Wassermann reaction was negative. Cephalin flocculation was persistently 4 +. The prothrombin time was 40 and 35 per cent of normal at eighteen day intervals. Total protein measured 7.62 Gm. with reversal of the albumin to globulin ratio. There was 14 per cent retention of sulfobromophthalein (bromsulphalein®) sodium. Tests for febrile antigens gave negative reactions on two occasions. Blood cultures on three occasions yielded no pathogenic growth. A culture of the urine was contaminated. The reaction to a skin test for trichinosis was strongly positive. A spinal tap revealed nothing abnormal.

Roentgenologic Appearance: A roentgenogram of the chest showed a moderate amount of fibrosis in both pulmonary fields and thickening of the apical cap on the right side. The heart was of normal size and configuration. Another roentgenogram taken twelve days later showed no changes. The following possibilities were considered: chronic passive congestion due either to cardiac disease or to chronic

bronchitis; pneumonoconiosis of some kind; fungous infection; possible old tuberculous disease and, very unlikely, alveolar carcinomatosis.

An excretory pyelogram was normal in appearance. There was elevation of the floor of the bladder by an enlarged prostate. A scout film of the abdomen showed nothing abnormal. The hands, feet and pelvis were examined and failed to reveal any evidence of either sarcoidosis or multiple myeloma. It was noted, however, that in the proximal phalanges of both hands the trabecular pattern was somewhat more prominent than usual, and similar accentuation of the trabecular pattern was suggested in the second phalanges of these fingers. These findings, however, could not be attributed either to sarcoidosis or to multiple myeloma and, therefore, other

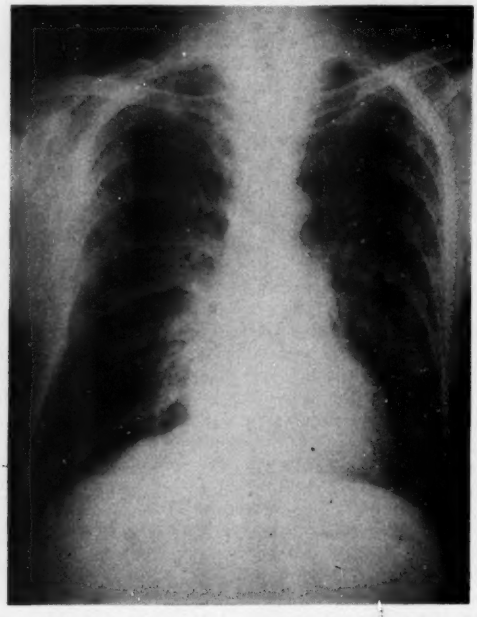

Fig. 1 (first admission).—Roentgenogram of the chest showing no definite lesion except for hilar shadows more pronounced on the right.

causes were searched for. A gastrointestinal series showed essentially normal conditions.

Course in the Hospital: The patient's temperature spiked almost every afternoon from normal to 101 or 102 F., gradually decreasing until he became almost afebrile. After forty days of hospitalization and treatment, the patient was discharged, with his condition slightly improved but otherwise unchanged.

Readmission.—On Nov. 11, 1949, the patient was readmitted to the hospital. He had remained home for approximately two months following his discharge from the hospital in January. He claimed his elevations in temperature subsided and he was able to return to work in April. The patient was asymptomatic at that time. He noticed a gradual loss of all finger nails during the early part of summer with subsequent replacement. His toe nails were now beginning to break off. He began

to note a daily elevation in temperature in October (to 100 and 101 F.) but was able to continue with his work. His appetite always remained good, and there was no evidence of loss of weight since his last admission. One week previous to readmission productive cough, weakness and increased elevation in temperature developed. The sputum became blood tinged several days before, concomitant with the appearance of loose "black" stools for the first time. The patient was not taking any medicament except diphenylhydantoin sodium and phenobarbital (one seizure had occurred since his discharge in January).

Results of Physical Examination: The physical examination revealed a well developed but emaciated white man. The positive observations were slight cyanosis

Fig. 2 (second admission).—Roentgenogram showing extensive lesions in both lungs that suggest neoplasm or infection with acid-fast organisms.

of the lips and finger nails; several small discrete lymph nodes in the left axilla and inguinal areas; moderate dyspnea; tachycardia; frequent cough with blood-tinged sputum; persistent rales at the base of the right lung with increased breath sounds, and questionable dulness at the bases of both lungs. The liver was palpated 3 to 4 fingerbreadths below the right costal margin and enlarged toward the umbilicus. It was nontender and the edges were smooth. The systemic review gave essentially normal results, except for frequency in urination, especially at night, and exertional dyspnea which was of recent origin. There was no pain in the chest. The elevation in temperature, unassociated with chills or profuse sweats, ranged from 101 to 105 F. The patient continued to have a high fever and died twenty days after his admission.

Laboratory Data: Urinalyses on November 12 and 22 showed the specific gravity to be 1.020 to 1.023. There were occasional white blood cells and reactions to tests for albumin and sugar were negative. Blood studies made on November 12 showed 13 Gm. of hemoglobin per hundred cubic centimeters, 4,400,000 red blood cells and 10,400 white blood cells per cubic millimeter, with 70 per cent polymorphonuclear cells and 30 per cent lymphocytes. Blood studies on November 17 revealed 4,200,000 red blood cells and 5,100 white blood cells, with 58 per cent

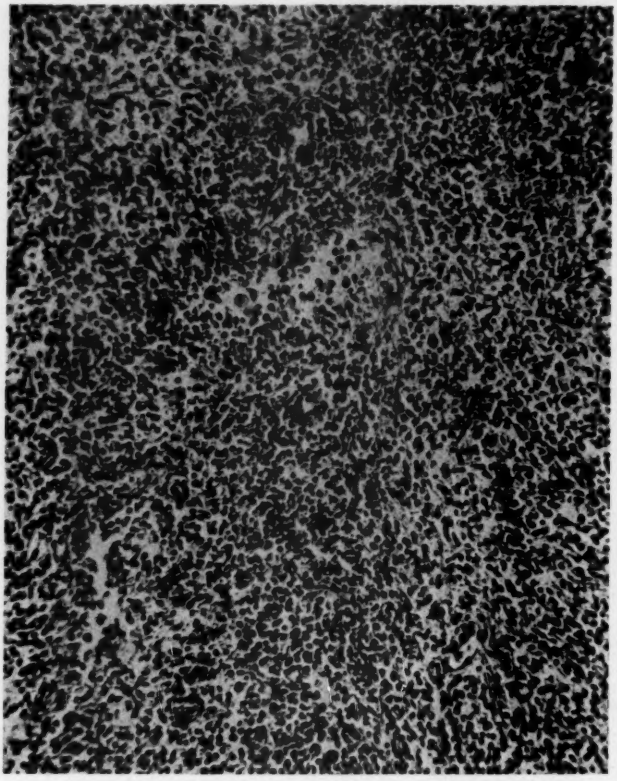

Fig. 3.—Section from lung showing extensive granulomatous lesions infiltrating alveoli and interspaces. Hematoxylin and eosin stain; × 100.

polymorphonuclear cells and 42 per cent lymphocytes. On November 28 a tuberculin skin test gave a negative reaction. Cultures of the blood yielded no growth. The serum was negative for febrile agglutinogens. In the sputum no acid-fast bacilli were seen, but an occasional Candida organism was present. A biopsy specimen of the liver showed chronic hepatitis. On electrocardiographic study sinus tachycardia, right axis deviation and vertical position of the heart were demonstrated.

Roentgenologic Appearance: The roentgenograms of the chest disclosed a serious involvement of both pulmonary fields. There were many small areas of infiltration which showed a tendency to coalesce in the middle and lower lobes of the right lung and the upper lobe of the left, presenting the appearance of a pneumonic process or an unusual tuberculosis. Over the rest of the lungs, however, the appearance was more suggestive of edema. At the right phrenocostal sulcus, there was a triangular area of increased density which suggested possible atelectasis. The

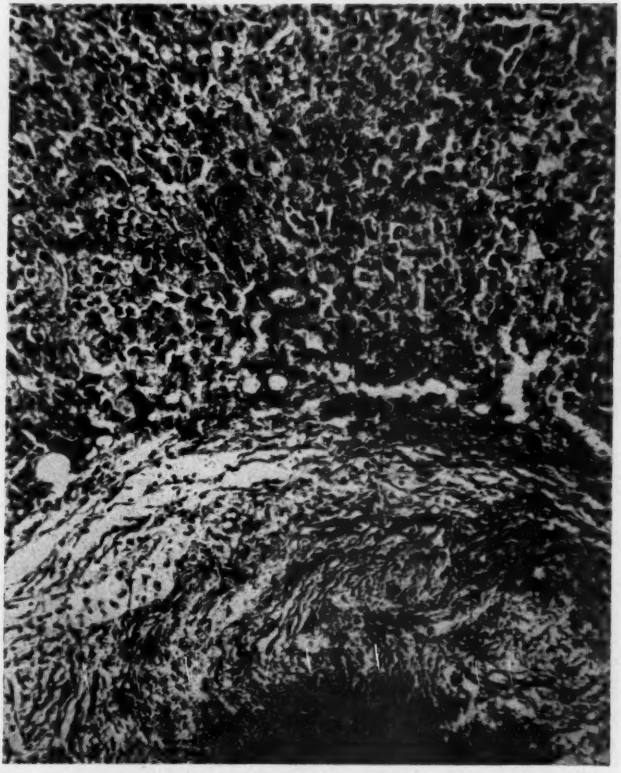

Fig. 4.—Granulomatous lesion surrounding a necrotic area. Hematoxylin and eosin stain; × 100.

roentgenographic appearance of the hands did not differ materially from that on the previous examination. There were some expansion of the cortex and accentuation of the normal trabecular pattern which suggested the possibility of one of the anemias, such as familial erythroblastic (Cooley's) or sickle cell anemia.

Autopsy Report.—Gross Examination: The body was that of a fairly well developed, poorly nourished 53 year old white man. There was no cervical or axillary adenopathy. Several small shotty glands could be palpated in the right

inguinal area, the largest being about 1 cm. in diameter. The chest was symmetric and dull to flat on percussion throughout. The abdomen was slightly distended and deeply tympanitic to percussion. No masses or organs could be palpated in the abdomen. The external genitalia were essentially normal in appearance. The extremities did not show any abnormalities or deformities.

When the chest was opened, there was 2,000 to 2,500 cc. of clear brownish fluid in the right pleural cavity. No fluid was present in the left side of the chest. No

Fig. 5.—Peribronchial lesion, the probable primary source. Hematoxylin and eosin stain; × 100.

adhesions of either lung were observed. The heart appeared normal in size and the pericardium contained a normal amount of clear straw-colored pericardial fluid. There was no gross neoplastic involvement of the mediastinal lymph nodes.

Lungs: The right lung weighed 960 Gm. Externally, it was grayish with alternate purplish mottled areas. In the lower lobe of the right lung there was a firm palpable mass approximately 8 cm. in diameter, not well demarcated from the

surrounding tissue. Scattered throughout the remainder of the lung were multiple tumors, the largest measuring 1 cm. in diameter. On section the mass in the base described previously consisted of alternate areas of whitish neoplastic material interspersed with anthracotic pulmonary tissue. The bronchial mucosa at the hilus was thickened and granular in appearance. The left lung weighed 690 Gm. Externally, it was essentially similar in appearance to the opposite lung. It con-

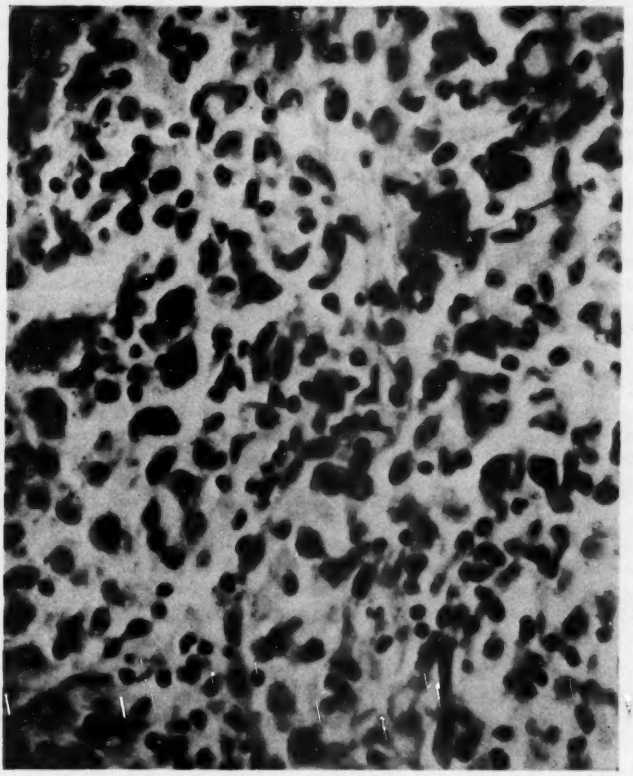

Fig. 6.—High power view of typical lesion showing pleomorphism, Sternberg-Reed cells, occasional eosinophils and reticular cells. Hematoxylin and eosin stain; × 400.

tained a tumor mass 4 cm. in diameter in the upper lobe. On section this mass was identical with that in the lower lobe of the right.

Heart: No external abnormalities were noted in the heart. The myocardium did not have any palpable areas of softening.

When the abdomen was opened, no free fluid was noted in the peritoneal cavity. All loops of bowel were moderately dilated. The abdominal organs were in their normal positions and maintained their relationships. There were no abdominal adhesions.

Liver: The surface of the liver contained multiple tubercle-like whitish masses, the largest being 2 mm. in diameter. There were also several retention cysts on the surface which contained clear, serous material. The gallbladder was white and atrophic.

Spleen: The surface of the spleen contained a whitish infarcted area. On section the cut surface showed congestion of the pulp with prominence of the malpighian corpuscles.

Kidneys: The kidneys were essentially normal in size. No enlarged retroperitoneal glands could be palpated.

The anatomic diagnoses were carcinoma of the lungs, right pleural effusion, bilateral lobar pneumonia, retention cysts of the liver and congestion of the spleen.

Cultures from autopsy material showed no acid-fast organisms. Routine culture showed a viridans streptococcus, Diplococcus pneumoniae, hemolytic Staphylococcus pyogenes var. aureus and Pseudomonas aeruginosa. No fungi were grown.

Microscopic Findings: Lungs: Sections of the lungs showed extensive infiltration of the alveoli, with filling by inflammatory cells, mostly composed of polymorphonuclear cells, fibrin and fragmented red blood cells. Further parts showed infiltration with pleomorphic cells, mostly reticular in type. Others were single and multinucleated giant cells resembling Sternberg-Reed cells. These cells had also infiltrated the peribronchial spaces and alveoli. Other parts showed advanced necrosis with hyaline degeneration. Special staining of the lung disclosed mostly reticular cells; no definite eosinophils could be identified. Occasional alveoli were left intact. The bronchioles were filled with purulent exudate. No microscopic evidence of primary bronchogenic carcinoma could be seen, in spite of the gross appearance of such a pathologic condition.

Spleen: Sections of the spleen did not reveal any evidence of infiltration with Hodgkin's type cells or of tuberculous infection. There were increased reticular cells and thickened trabeculae. Moderate arteriosclerotic changes were noted in the terminal vessels.

Kidneys: Sections of the kidneys showed fairly well preserved glomerular tufts and tubules, except for moderate congestion of the capillaries. The blood vessels revealed moderate arteriosclerotic changes. There was increased fibrous stroma of the medulla.

The histologic diagnoses were primary Hodgkin's disease of the lungs and the presence of occasional Hodgkin's nodules in the liver.

COMMENT

This case showed variations in both antemortem and postmortem diagnoses. At his first admission, the patient apparently had a virus infection affecting the liver and kidneys with little involvement of the lungs. The biopsy specimen of the lymph node did not reveal any lesion resembling that of Hodgkin's disease and the biopsy specimen of liver also failed to show any type of granulomatous lesion, but some inflammatory reaction was noted comparable to mild infectious hepatitis. Little importance was attached to the positive reaction to the trichinosis skin test, which may have been nonspecific in type.

On his second admission, the entire picture changed. There were definite pulmonary symptoms and the roentgenologic appearance was of some indefinite lesion involving both lungs. Various diagnoses were

suggested at that time, such as sarcoidosis, miliary tuberculosis, mycotic infection and diffuse alveolar carcinomatosis. In spite of the septic type of temperature elevation, repeated blood cultures and sputum studied yielded no pathogenic organisms or fungi. The changes in the phalangeal bones, such as rarefaction, suggested sarcoidosis or multiple myeloma, but this was not proved. There was no definite antemortem diagnosis. Postmortem observations were as puzzling and indefinite as antemortem findings. It was most unusual not to find any involvement of the mediastinal lymph nodes, in spite of extensive bilateral pulmonary lesions. The retroperitoneal lymph nodes were not enlarged. The pulmonary lesions grossly simulated diffuse so-called alveolar carcinomatosis or unresolved lobar pneumonia. The final diagnosis was reached only after the histologic study of the sections, which were mostly composed of pleomorphic cells with numerous Sternberg-Reed cells, reticuloendothelial cells and a few eosinophils, more prominent at the peribronchial areas, with infiltration also of the alveolar walls and interalveolar spaces. There was also secondary inflammatory reaction, with exudate in the alveoli mostly composed of polymorphonuclear cells and resembling that of pneumonic consolidation.

The review of the literature of the last few decades showed few authentic cases of primary pulmonary Hodgkin's disease. The majority on record are those secondary to mediastinal or retroperitoneal Hodgkin's disease. The reported cases show definite evidence that peribronchial lymph nodes are the probable source of Hodgkin's granulomatosis. Extension of the lesion of the parenchyma of the lung was postulated to be through the lymphatics or capillaries.

Hartfall [6] in his article on the subject of Hodgkin's disease of the lung stated: "The lung parenchyma is one of the least common situations in which the lesions may occur. When a clinical condition suggests tuberculosis and x-ray suggests neoplasm of the lung, the observer should consider lymphogranuloma (Hodgkin's disease of the lung)." Terplan [7] also expressed a similar opinion, that primary lymphogranulomatous foci within the lung are too rare as phenomena to permit any conclusions to be drawn regarding pulmonary manifestations such as in our case.

Pulmonary involvement in Hodgkin's disease is fairly common. Henke and Lubarsch [5] placed the incidence above 40 per cent. Moolten [3] stated in his report of 18 cases of Hodgkin's disease with postmortem examination that 9, or 50 per cent, showed pulmonary lesions; but these authors did not give any information in regard to the number in

6. Hartfall, S. J.: Hodgkin's Disease of the Lung, Guys Hosp. Rep. **82**:55, 1932.

7. Terplan, K.: Ueber die intestinale Form der Lymphogranulomatose, Virchows Arch. f. path. Anat. **137**:241, 1922.

which the primary focus was in the lung. The reports of seven of the authors cited by Falconer and Leonard [1] showed the incidence of pulmonary involvement to be 40 per cent.

Our case is unique in comparison with the cases thus far reported in that the liver and spleen were minimally involved and the disease was of only two months' duration. The lungs were the main focus of the lesion. No involvement of the lymph nodes was seen. The course was of the acute fulminating type, such as one would expect in acute infectious disease. The anemia often seen in Hodgkin's disease was strikingly lacking in this case. This probably was due to the acute course with no invasion of bone marrow.

Summary of Previous Reports of Pulmonary Hodgkin's Disease, According to Falconer and Leonard [1]

Author	Total Number of Cases	Number with Pulmonary Involvement	Per Cent
Ceelen-Rabinowitsch	10	4	40.0
Herxheimer	8	5	61.0
Sternberg	15	5	33.0
Weinberg	7	2	28.0
Versé	16	6	37.0
Moolten	18	9	50.0
Whitaker	22	7	32.0
Authors [Falconer and Leonard]	29	9	31.0
Total	125	47	37.6

SUMMARY AND CONCLUSION

An authentic case of primary Hodgkin's disease of the lung is reported because of its rarity and the rapid course of the disease. A diagnostic problem during the illness was presented in spite of roentgenologic studies and biopsy of a lymph node. No antemortem diagnosis could be made.

Review of the literature of the last thirty years revealed many instances of pulmonary Hodgkin's disease but few were definitely proved cases of primary type. A large majority of the cases were of secondary involvement.

The probable source of Hodgkin's disease is the peribronchial lymphatics in which reticular cells predominate. Many more cases of primary pulmonary Hodgkin's disease have perhaps occurred, but were not reported because postmortem studies were not made or because diffuse involvement of the lymphatic system and other organs made it impossible to decide which of the organs was the primary focus.

Photographs were made by Albert Levin, F.B.P.A.

PRIMARY ATYPICAL AMYLOIDOSIS

Report of a Case

W. NOEL WHITTLESEY, M.D.
NEW YORK

AMONG NEARLY 3,200 autopsies performed at St. Vincent's Hospital over a period of fifteen years, 5 cases of amyloidosis were discovered, 1 of which is believed to be a clearcut example of the primary atypical form. The purpose of this paper is to attempt to justify the use of the term "primary atypical" as accurately descriptive of this type of amyloid disease.

Three factors have made satisfactory classification of amyloidosis difficult. The first is the confusing variety of terms employed by authors in describing their cases; the second is the wide variation in anatomic distribution of the amyloid revealed at autopsy; the third, and probably most fundamental, is the fact that little is known of the immediate cause, or causes, of the deposition of amyloid in the tissues.

To date, approximately 70 cases belonging in the category of primary amyloidosis have been reported in the literature. Terminology used by the various authors includes "primary," [1] "primary systemic," [2] "primary atypical," [3] "idiopathic," [4] "atypical," [5] "generalized," [6] "diffuse" [7] and

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From the Department of Pathology, St. Vincent's Hospital.

1. (*a*) Binford, C. H.: Primary Amyloid Disease of Myocardium and Blood Vessels: Report of Case with Death from Myocardial Failure, Arch. Path. **29**:314-320 (March) 1940. (*b*) Dahlen, D. C.: Am. J. Path. **25**:105-122 (Jan.) 1949. (c) Reimann, H. R.; Koucky, R. F., and Eklund, C. M.: ibid. **11**:977-988 (Nov.) 1935. (*d*) Larsen, R. A.: ibid. **6**:147-159 (March) 1930.

2. (*a*) Golden, A.: Primary Systemic Amyloidosis of Alimentary Tract, Arch. Int. Med. **75**:413-416 (June) 1945. (*b*) Hartney, J. B.; Biederman, A. A.; Blumberg, J. M., and Leedham, C. L.: Primary Systemic Amyloid Disease: Report of Case Emphasizing Cardiac Involvement, Arch. Path. **47**:598-611 (June) 1949. (*c*) Iverson, L., and Morrison, A. B.: Primary Systemic Amyloidosis, ibid. **45**:1-20 (Jan.) 1948. (*d*) Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis: Involvement of Cardiac Valves, Joints and Bones, with Pathologic Fracture of Femur, ibid. **27**:267-288 (Feb.) 1939. (*e*) Lindsay, S.: Am. Heart J. **32**:419-437 (Oct.) 1946. (*f*) Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, Arch. Path. **39**:315-322 (May) 1945.

3. Ferris, H. H.: Am. J. Path. **12**:701-718 (Sept.) 1936.

4. (*a*) Christian, H.: M. Clin. North America **15**:805-811 (Jan.) 1932. (*b*) Kerwin, A. J.: J. Lab. & Clin. Med. **22**:255-260 (Dec.) 1936.

(Footnotes continued on next page)

"para-amyloidosis."[8] However, there has been general agreement concerning what constitutes primary amyloidosis, that is, absence of tuberculosis, chronic suppurative disease or other disease assumed to cause the deposition of amyloid.

Practically all these cases have one feature in common. Some aspect of each—clinical or anatomic—differs from the observations in amyloidosis associated with tuberculosis. Wilks[9] in 1856 apparently was the first to recognize the existence of this entity. In discussing "lardaceous disease," he placed those cases not associated with other disease in a class by themselves.

In 1929 Lubarsch[10] reported and discussed a group of cases showing deposits of amyloid in unusual locations. He noted that this group had certain characteristics: relative freedom of spleen, liver, kidneys and adrenal glands from amyloid and presence of deposits in other organs and tissues; deposition of amyloid as discrete nodules in some cases; failure often of reaction to the well known tests for amyloid; absence of demonstrable concomitant infection. These criteria have in general been accepted by later authors in reporting their cases, some of them calling this disorder "primary" amyloidosis,[11] others preferring the term "atypical" amyloidosis.[5b, c]

In 1935, Reimann, Koucky and Eklund[1c] proposed the following classification: (1) primary amyloidosis, (2) secondary amyloidosis, (3) tumor-forming amyloidosis and (4) amyloidosis with multiple myeloma. Their criteria for the recognition of the primary type were similar to those of Lubarsch. Tumor-forming amyloidosis is primary in nature but was considered to be sufficiently distinct to form a class by itself. They stated that amyloidosis with multiple myeloma is secondary in nature but has a distribution characteristic of the primary type. They admitted that this grouping is unsatisfactory, inasmuch as there is frequent overlapping of group characteristics. This classification, based chiefly on the presence or absence of an etiologic factor, is given also by Koletsky and Stecher[2d] and Lindsay and Knorp[2f] in their reviews of the literature.

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5. (*a*) Humphries, E. C.: Atypical Amyloidosis, Arch. Path. **17**:134 (Jan.) 1934. (*b*) King, L. S.: Am. J. Path. **24**:1095-1115 (Sept.) 1948. (*c*) Perla, D., and Gross, H.: ibid. **11**:93-112 (Jan.) 1935.

6. Warren, S.: Am. J. Path. **6**:161-167 (March) 1930.

7. Bannick, E. G.; Berkman, J. M., and Beaver, D. C.: Diffuse Amyloidosis: Three Unusual Cases; Clinical and Pathologic Study, Arch. Int. Med. **51**:978-990 (June) 1933.

8. Strauss, A.: Virchows Arch. f. path. Anat. **291**:219-236, 1933.

9. Wilks, S.: Guy's Hosp. Rep. **2**:103-132, 1856.

10. Lubarsch, O.: Virchows Arch. f. path. Anat. **271**:867-889, 1929.

11. Dahlen.[1b] Reimann and others.[1c] Koletsky and Stecher.[2d] Lindsay and Knorp.[2f]

Perla and Gross [5c] in 1935 reported 3 cases of atypical amyloidosis, in none of which was any etiologic factor demonstrated. The term "atypical" here apparently refers to the case as a whole and not to anatomic distribution of amyloid in particular.

Other authors were of the opinion that difference in anatomic distribution constitutes a sounder basis for classification of amyloid disease than any other single factor. Humphries [5a] reported in 1934 a case of atypical amyloidosis showing what she considered to be an atypical distribution of amyloid in liver and kidneys. In 1948, King [5b] reported 6 cases of atypical amyloidosis with deposits in the heart and small blood vessels. He discussed the difficulties involved in establishing criteria for the classification of amyloidosis and proposed the following:

1. Typical amyloidosis (distribution in spleen, liver, kidneys and adrenal glands)
   - (*a*) Associated with other disease
   - (*b*) Not associated with other disease
2. Atypical amyloidosis (distribution in other organs)
   - (*a*) Associated with other disease
   - (*b*) Not associated with other disease

In the classic secondary type of amyloidosis deposits commonly appear in the parenchyma of spleen, liver, kidneys and adrenal glands.[12] This may be considered typical distribution. Deposits of amyloid in these organs in other than parenchymal sites (in the walls of arterioles, for example) or in other organs and tissues may be referred to as atypical distribution. Many cases in which there is an atypical distribution also show amyloid in some or all of the typical sites. For instance, in Ferris' [8] case of amyloidosis of heart, lungs and blood vessels deposits were also seen in the spleen and adrenal glands. Gerber's [13] case of amyloidosis of the bone marrow included large deposits in spleen, liver, kidneys, adrenal glands and other organs.

Primary amyloidosis with typical distribution is not uncommon. A patient reported on by Christian [4a] in 1932 had deposits in liver, spleen, kidneys and adrenal glands. He died of renal failure due to the amyloid. Several similar cases are on record. On the other hand, secondary amyloidosis with atypical distribution has been reported. In the case of Spain and Barrett,[14] associated with infected bronchiectasis, deposits were demonstrated in the heart, larynx and small blood vessels.

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12. Dahlen, D. C.: Ann. Int. Med. **31**:105-119 (July) 1949.

13. Gerber, I. E.: Amyloidosis of the Bone Marrow, Arch. Path. **17**:621-630 (May) 1934.

14. Spain, D. M., and Barrett, R. C.: Amyloidosis in Atypical Sites (Cardiac Valves, Larynx), Arch. Path. **38**:203-206 (Oct.) 1944.

This brief discussion illustrates the fact that typical and atypical distribution patterns often overlap and that, as Hartney and his associates [2b] pointed out, difference in distribution alone is not sufficient to constitute a line of demarcation between primary and secondary amyloidosis. However, in the vast majority of instances the general pattern of amyloid distribution in the group of cases under discussion is clearcut and conforms to that originally described by Lubarsch.

I do not propose to discuss at length the problem of etiology, but a few words on the subject may well be said here. The factors leading to the deposition of amyloid in tissues are not fully understood and the use of the terms "primary" and "secondary" may, therefore, seem premature. However, in the present state of knowledge, the use of these terms is justifiable on the ground that they indicate the absence or presence, respectively, of a disease which has often been observed to be associated with amyloid deposition. A simple classification, therefore, would be the following:

Primary amyloidosis (not associated with a disease)
- Typical
- Atypical

Secondary amyloidosis (associated with disease)
- Typical
- Atypical

REPORT OF CASE

A 65 year old white man was admitted to St. Vincent's Hospital on Aug. 10, 1949. He had apparently been in good health until six weeks before his admission. At that time he noted pain in the lumbar region which became progressively worse, ultimately confining him to his bed. Subsequently his hands became swollen and painful. He had attacks of vomiting, became anuric and lapsed into semistupor. The past history contained nothing significant.

Physical examination revealed an elderly white man, stuporous, restless and uncooperative. Blood pressure was 105 systolic and 55 diastolic. Respirations were 52 per minute and the temperature was 106 F. His heart was not enlarged to percussion; the heart rate was 140 and regular. There were rales at the bases of both lungs. His abdomen was moderately distended and the liver was palpable. There was no edema of the left leg; the right leg had been amputated.

An electrocardiogram showed low voltage, R-T depression and slight slurring of the QRS complexes. The hemoglobin concentration was 100 per cent. There were 4,700,000 red blood cells and 19,000 white blood cells, with 75 per cent polymorphonuclear leukocytes and 19 per cent lymphocytes. Blood cultures yielded no pathogens. Blood chemical studies showed 220 mg. of sugar, 1.8 mg. of creatinine, 44 mg. of urea nitrogen and 0.9 mg. of bilirubin. The erythrocyte sedimentation rate was 6 mm. in two hours. The blood Kahn reaction was negative. The urine showed a 2+ reaction for albumin and a 1+ reaction for sugar. A spinal tap produced clear fluid containing 42 lymphocytes, 151 mg. of sugar and 62 mg. of protein.

He was treated with fluids intravenously, penicillin and streptomycin. However, he remained comatose and died thirty-two hours after his admission.

Necropsy Observations.—Gross Examination: An autopsy was performed seven hours after death. Gross observations of significance were limited to the heart. This organ was moderately enlarged and weighed 450 Gm. Both ventricles were moderately hypertrophied and dilated. The myocardium was of normal firm consistency throughout but had a grayish to brownish mottled appearance, most noticeable in the interventricular septum. The endocardium and valves were normal.

Fig. 1.—Amyloid in the myocardium. Congo red stain; × 60.

Microscopic Examination: Sections from all organs were prepared and stained with hematoxylin and eosin. The lesions to be described were noted in the heart and lungs only.

Throughout the myocardium, but most remarkable in the interventricular septum, there were numerous deposits of a homogeneous, eosinophilic material which stained pink with congo red and reddish purple with methylrosaniline chloride (methyl violet), reactions considered to be characteristic of amyloid (fig. 1). Most of the deposits were large, irregular nodular masses located characteristically in the vicinity of arterioles. Within these could occasionally be seen an isolated nucleus or an atrophied muscle fiber, suggesting replacement of muscle

by amyloid. Occasional small spaces lined with flat nuclei were seen, indicating involvement of blood vessels. In most sections the masses gave no clear indication of their origin.

From these masses thin strands could be traced out along the reticulum, in many places completely surrounding the individual muscle fibers or surrounding the spaces left by atrophied fibers. The deposits on the reticulum were extensive in some areas, minimal in others. There were also many thick, nodular strands

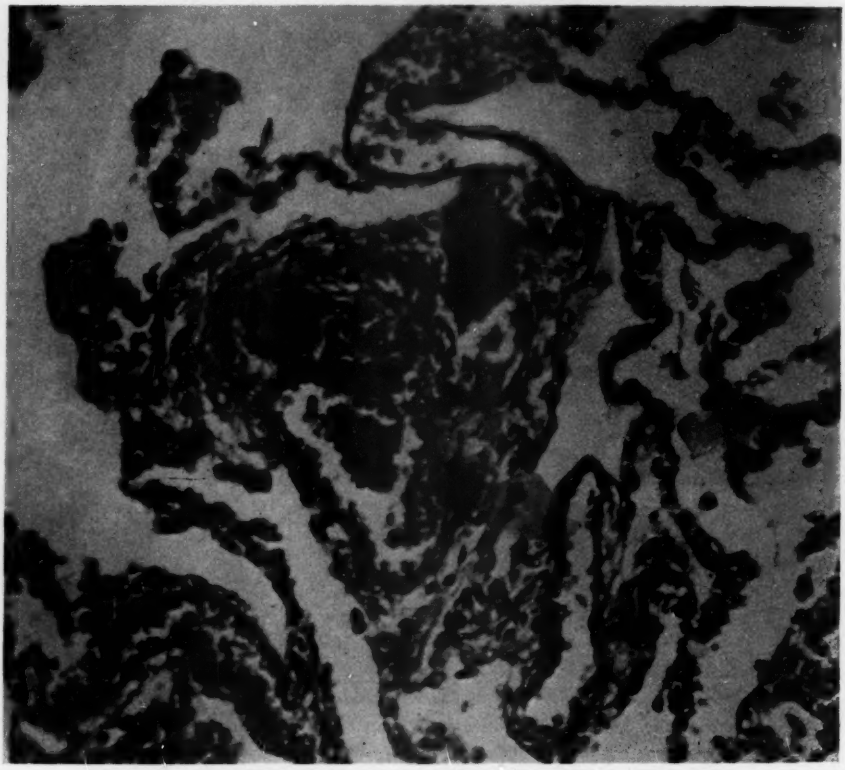

Fig. 2.—Amyloid in wall of arteriole of lung. Congo red stain; × 80.

which appeared to run across the grain of the myocardium, representing involved arterioles. However, most of the interstitial amyloid was concentrated in the larger masses.

Amyloid deposits were seen in the walls of many of the arterioles. Some were in the form of thin, annular strands or nodular masses in the adventitia or media with no apparent diminution in the size of the lumen. Others entirely replaced the vessel wall, with thickening and various degrees of stenosis. Amyloid was seen beneath the endothelium of dilated capillaries.

There were many isolated small nodular deposits in the interstitial tissues. Some of these were connected by thin strands of amyloid to the deposits observed in the arterioles. A few small irregular deposits were seen beneath the endocardium.

Associated widespread degeneration of the myocardium was present, which seemed to be out of proportion to the actual amount of amyloid present. In many areas vacuolation of the muscle fibers was conspicuous; in others fibers had disappeared, leaving a loose network of stroma. Some muscle cells had a pinkish color when stained with congo red, but there was no direct evidence of invasion of the cells by amyloid from the surrounding reticulum, such as was described by Larsen.[1d] In all locations the amyloid stained well with congo red. The central portions of the deposits were definitely pink, while the periphery stained more darkly, in some parts approaching orange-red. With methylrosaniline chloride the characteristic reddish purple color was obtained, but it was not uniform. Sections stained with iodine and sulfuric acid did not give a characteristic reaction. The amyloid could not be successfully stained with the silver method described by King.[5b]

Examination of congo red preparations from other organs revealed the amyloid material only in the lungs (fig. 2). Occasional small deposits in the walls of arterioles were seen.

Gross and microscopic examination of the brain failed to reveal deposition of amyloid or any other pathologic lesion.

COMMENT

Involvement of the heart in primary amyloidosis is common. In reviewing the literature of the disease up to 1946, Lindsay[2e] found amyloid described in the heart in 39 of 45 cases. In 32 of these clinical evidence of heart failure was reported. In all those cases in which electrocardiographic studies were made there was evidence of myocardial damage. In retrospect, the enlarged liver and the anuria observed in the case under discussion may have pointed to a diagnosis of heart failure, though direct clinical evidence of this condition was absent. However, definite electrocardiographic evidence of damage to the myocardium was obtained.

In cases of primary amyloidosis involving the heart, extensive deposits have usually been demonstrated in other organs. Binford[1a] and Dahlen[1b] reported cases in which amyloid was detected only in the heart and small blood vessels throughout the body. The observation of amyloid deposition limited to the heart and vessels of the lungs, as appears to be the case in the present instance, is uncommon, only one report having been found. An 88 year old man, reported on by King,[5b] showed amyloid in the heart and vessels of the lungs only; there was an associated severe degree of atherosclerosis of the aorta, with occlusion of the superior mesenteric artery, and death resulted from infarction of the intestine. Senility was considered as a possible cause of the deposition of amyloid.

Microscopically, the striking feature of this case was the presence of large, irregular, well isolated masses of amyloid associated with extensive degeneration of the myocardium. Similar masses have been described in a few cases.[15] In most cases interstitial amyloid deposits have been diffuse, surrounding the individual muscle fibers with amyloid rings.[2e] In the present instance relatively little interstitial deposit was seen, most of the amyloid being concentrated in the larger patches. The observation of small, apparently isolated deposits connected by strands of amyloid to vascular lesions appears to bear out the contention of Larsen [1d] that amyloid is deposited originally in relation to blood vessels; he was able to demonstrate such connections by means of serial sections. Giant cells, occasionally reported in amyloidosis,[2c] were not seen in the present case.

In discussing the ways in which amyloid in the myocardium can produce heart failure, Lindsay emphasized the role of the interstitial deposits in compressing and damaging the muscle fibers, resulting in degeneration, atrophy and necrosis. He also considered that narrowing of the vessels by amyloid, with consequent diminution of blood supply, was important.

The fact that in this case the amyloid gave characteristic reactions to some of the specific stains and not to others agrees with the observations of other authors. Lindsay [2e] reported good staining reactions to congo red and methylrosaniline chloride and no reaction to iodine and sulfuric acid. Identical results were obtained in the present case. Reimann and his co-authors [1c] reported typical staining with methylrosaniline chloride but not with congo red or iodine.

SUMMARY

The classification of amyloid disease is briefly discussed. A case of primary atypical amyloidosis involving the heart and the vessels of the lungs is reported.

15. Hartney and others.[2b] Kerwin.[4b] Perla and Gross.[5c]

HIATUS HERNIA

Analysis of Twenty-Five Cases

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THIS REPORT consists of a brief analysis of 25 cases of hiatus hernia. Individual case reports are given to illustrate various complications, associated conditions and difficulties in differential diagnosis. Thirteen of these cases are from our services at the University of Nebraska College of Medicine, and 12 are from our private practice. All the latter have been seen during the past two years.

DEFINITION

The term hiatus hernia as used in this report refers to the type of esophageal hiatus hernia seen in adults as a result of a sliding herniation of the stomach into the thoracic cavity. No attempt has been made to differentiate between paraesophageal hiatus hernia, in which the lower part of the esophagus remains in its normal position and a portion of the cardiac end of the stomach herniates through the hiatus alongside the esophagus, and esophagogastric hernia, in which the lower end or abdominal part of the esophagus also prolapses through the hiatus. Some of these patients appeared to have a congenitally short esophagus, but this factor is difficult to evaluate, for, as Bockus [1] pointed out, it is uncertain in most of these patients whether the short esophagus preceded the hernia or whether the esophagus shortened secondarily as a result of the hernia. Further, a shortening of the esophagus as a result of vagal irritation from esophageal or abdominal sources may be implicated in the actual production of the hernia, as well as in its continuance. We do not propose to discuss the various other types of diaphragmatic hernia.

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1. Bockus, H. L.: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1943, vol. 1, pp. 151-167.

PATHOGENESIS

There is probably a congenital weakness or maldevelopment of the diaphragm in many patients with hiatus hernia, but the fact that most of these hernias do not develop until late in life suggests to many authorities that circumstances which greatly increase intra-abdominal pressure are important in their production. Such circumstances may be a known or a long-forgotten episode of trauma to the chest or abdomen, pregnancy, ascites, coughing, vomiting, straining at stool or even the wearing of a tight corset. Some hiatus hernias which occur late in life may be due to a loss of fat tissue and decreased elasticity of connective tissue in the diaphragm and about the esophageal hiatus, which allow displacement of the muscle fibers and protrusion of the stomach through the relaxed hiatus.

SEX

The sex incidence of hiatus hernia is variously reported to be 2 to 10 in women to 1 in men.[2] The 25 patients reported on here were not selected in regard to sex and are reported as they came to our attention. There were 13 men and 12 women in this group. However, the group is much too small to permit a reliable opinion concerning sex incidence.

BUILD

Most patients with hiatus hernia are said to be overweight. Nine of the 12 women included in this report were frankly obese. Only 1 of the 13 men was obese. However, it should be noted that most of the hernias were discovered only after the patients had reached advanced years and many may well have been obese when they were younger.

AGE

The youngest patient in this group was 22 years of age and the oldest 71. The average age was 58 years and the mean age approximately 61 years. This agrees with the published reports of larger groups which indicate that the great majority of persons with hiatus hernia are more than 50 years of age at the time the hernia is discovered. Kirklin and Hodgson [2d] stated that 92 per cent are over the age of 40 years.

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2. (*a*) Harrington, S. W.: Hiatus Hernia: Roentgenologic Considerations in Diagnosis and Treatment, Am. J. Roentgenol. **49**:185-196 (Feb.) 1943. (*b*) Ohler, W. H., and Ritvo, M.: Hiatus Hernia: Clinical Study, New England J. Med. **229**:191-196 (July 29) 1943. (*c*) Bockus.[1] (*d*) Kirklin, B. R., and Hodgson, J. R.: Roentgenologic Characteristics of Diaphragmatic Hernia, Am. J. Roentgenol. **58**:77-101 (July) 1947.

SYMPTOMS

The most consistent symptoms which occurred in these patients are shown in the accompanying tabulation:

Symptom	No. of Patients	% of Patients
Pain and/or distress	20	80
Regurgitation and/or vomiting	17	68
Fulness, gas and belching, usually worse after eating	15	60
Anemia with or without hematemesis and melena	11	44

Although this is a relatively small series of patients, the incidence of the various symptoms agrees almost exactly with the textbook descriptions and with published reports of many larger series.[3]

Various other symptoms are reported to be commonly associated with hiatus hernia. Dysphagia may occur, especially when the hernia is complicated by esophagitis or ulceration. This was noted in 4 of our patients. Pyrosis, or acid regurgitation, was complained of by 6. Singultus, or hiccup, has not been commonly reported but occurred as a severe symptom in 2 of this group and was the only symptom in 1. The symptoms may imitate those of peptic ulcer, gallbladder disease, cancer of the stomach, various forms of heart disease—especially angina pectoris—and organic pulmonary disease with cough and dyspnea.

The occurrence of anemia, with or without gross hematemesis or melena, in association with hiatus hernia is of great importance. Symptoms or signs of anemia may be the only manifestation of the hernia, as it was in 2 of our patients. Hematemesis or melena may be massive and seriously endanger life, as in 3 of these patients. Bleeding has been reported to occur in 25 to 40 per cent of hiatus hernias. Ohler and Ritvo [2b] reported 12 cases of gross bleeding (hemoglobin concentration of 50 per cent or less) and 29 cases with mild hemorrhage among 104 cases of hiatus hernia. Murphy and Hay [3b] reported 16 cases of severe anemia attributable to the hiatus hernia among their series of 72.

The symptoms most characteristic of patients with hiatus hernia are the following: Epigastric or substernal pain occurs after meals in association with fulness, gas and distress, is aggravated by reclining or perhaps comes on only at night and is relieved at least partially by getting up

3. (*a*) Higgins, W. H.: Medical Aspects of Hiatal Hernia: Review of 63 Cases, South. M. J. **36**:273-276 (April) 1943. (b) Murphy, W. P., and Hay, W. E.: Symptoms and Incidence of Anemia in Hernia at Esophageal Hiatus, Ann. Int. Med. **72**:58-63 (July) 1943. (*c*) Gilbert, N. C.; Dey, F. L., and Rall, J. E.: Recurrent Hiatus Hernia, J. A. M. A. **132**:132-134 (Sept. 21) 1946. (*d*) Adams, R., and Lee, W. F., Jr.: Hiatus Hernia: Clinical Report of 34 Surgically Treated Cases, S. Clin. North America **26**:742-750 (June) 1946. (*e*) Radloff, F. F., and King, R. L.: Esophageal Hernia, Gastroenterology **9**:249-252 (Sept.) 1947. (*f*) Harrington.[2a] (*g*) Ohler and Ritvo.[2b] (*h*) Bockus.[1]

and walking about; the pain or distress is often followed by regurgitation or vomiting not associated with nausea; hematemesis, melena and anemia, alone or in combination, are important and common.

PHYSICAL FINDINGS

Eleven patients, or 44 per cent of this group, showed distinct tenderness in the uppermost portion of the epigastrium on physical examination. Six had definite muscle guard in this area. These signs have not been reported commonly in the literature and are worthy of note. They are not specific, of course, but do emphasize the fact that unusual tenderness or muscle guard elicited on routine examination should not be ignored, even in the absence of symptoms. One of our patients showed this distinct tenderness but had no symptoms from her hiatus hernia during the seven years it was known to have been present.

ROENTGENOLOGIC APPEARANCE

Roentgenologic study is essential, not only to the diagnosis of hiatus hernia but also for determination of the type and extent of herniation and recognition of complicating or associated lesions. Hiatus hernias, which comprised 98 per cent of all diaphragmatic hernias seen at Mayo Clinic in 1944, can be grouped under three classifications, according to Kirklin and Hodgson.[2d] Esophageal hiatus hernia with redundancy of the lower part of the esophagus comprised 67 per cent of their cases. Esophageal hiatus hernia with shortened esophagus represented 26 per cent; according to Harrington,[2a] at operation the esophagus readily resumes normal length in more than 90 per cent of such cases. The congenitally short esophagus is rare and cannot be reliably differentiated roentgenologically. Paraesophageal hernia, with the lower portion of the esophagus lying alongside the herniated cardia, represented about 7.5 per cent of their cases. In this type, the esophagogastric junction remains below the diaphragm, whereas in the other types it slides upward into the hernial sac.

Complicating conditions, such as ulcer in the cardiac pouch, cancer in the intrathoracic portion of the stomach, esophagitis, stricture and obstruction are most readily apprehended by roentgenologic examination. Esophagitis and ulceration are somewhat commoner in association with hiatus hernia, apparently because of more reflux of gastric juices into the lower part of the esophagus and greater retention of secretions in the hernial pouch. Such inflammatory changes may give rise to stricture of the lower part of the esophagus. Cancer seems to be somewhat commoner, as do also achlorhydria and anemia in patients with hiatus hernia. Two of this series of patients had carcinoma in the cardiac portion of the stomach. Diverticula of the duodenum and jejunum, and to some extent of the colon, are commonly associated with hiatus

hernia, both conditions resulting from congenital weaknesses accentuated by the atrophies of middle age. Three of the patients in this series showed diverticula of the duodenum and/or jejunum. Small hiatus hernias may, on rare occasion, result from shortening of the esophagus by inflammatory or neoplastic changes, or rarely from the tug by a mediastinal tumor. The independent occurrence of unrelated diseases, such as cholecystitis, duodenal ulcer and lymphosarcoma, in this small series of patients emphasizes the need for constant alertness in searching the patient for other significant and sometimes more serious lesions.

The roentgenologic diagnosis of hiatus hernia is based on exact location of the esophagogastric junction above the diaphragm or the recognition of a saccular protrusion of the cardia above the diaphragm. Retardation of the barium sulfate stream at the esophagogastric junction and tortuosity of the lower part of the esophagus without dilatation may assist in diagnosis. The examination is best conducted with the patient rotated obliquely, with the right side forward about 30 degrees, while drinking a thick barium sulfate mixture. The demonstration of hiatus hernia is more apparent with the stomach filled and the patient recumbent, either in the Trendelenburg position or supine with the head lowered. Repeated examinations are often necessary, particularly with small hernias of the cardia, since the hernia may occur intermittently through the widened hiatus. Small hernias may at times be simulated by transient dilatation of the lower part of the esophagus ahead of a wave of peristalsis, best differentiated fluoroscopically as the barium sulfate mixture passes through the esophagogastric orifice. Large hiatus hernias may show up in a roentgenogram of the chest as retrocardiac masses, widening of the mediastinum or fluid levels. Ingestion of a few swallows of barium sulfate solution immediately demonstrates the intrathoracic herniation of the stomach in such cases.

TREATMENT

Hiatus hernia may present no symptoms and require no treatment. Those symptoms due to the mechanical nature of the hernia are best treated medically. The nature of the condition and the manner in which it causes symptoms should be carefully explained to the patient, together with an appropriate amount of reassurance. He should be advised to avoid coarse, rough foods; to chew his food well and to eat slowly; to avoid eating large meals and rather to eat more frequent smaller meals as required to maintain nutrition, and to stay upright for at least one to two hours after each meal. Food should not be taken at bedtime. Distressing nocturnal symptoms may be relieved by elevating the head of the bed to an angle of 30 degrees. Administration of antispasmodic, sedative and antacid drugs is often useful.

In spite of the fact that surgical repair should offer a complete cure for the condition, all authors on the subject agreed that surgical treatment is rarely necessary. It is a well standardized procedure but a formidable one, especially when one considers that the great majority of patients are in the older age group. We believe that surgical repair may be indicated or seriously considered for patients who have had repeated serious bleeding, for patients who are seriously disabled by pain or other symptoms not responding to medical measures and for those few patients in whom the symptoms and signs may be confused with associated or complicating conditions in the region of the hernia which of themselves require surgical treatment.

Three of our group of 25 patients underwent surgical treatment, all with good results. One of these was found to have a lymphosarcoma

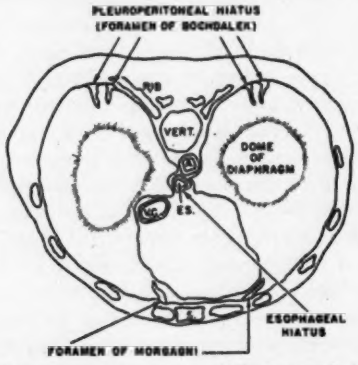

Fig. 1.—Sites of spontaneous occurrence of diaphragmatic hernia: Esophageal hiatus, 97 per cent; pleuroperitoneal hiatus (foramen of Bochdalek), 2 per cent; foramen of Morgagni, 1 per cent.

of the stomach with a large gastric ulcer, and a subtotal gastric resection was done as well as repair of the hernia. The results of surgical treatment are uniformly reported as good by other authors.[4]

REPORT OF CASES

Case 1.—K. A., a 53 year old white woman, presented herself for routine physical examination. She had no symptoms but was known to be diabetic and had been taking 20 units of protamine zinc insulin injection U. S. P. daily for several years. She was moderately obese. Examination of the abdomen revealed the

4. McNealy, R. W., and McCallister, J. W.: Symposium on Clinical Advances in Surgery: Transabdominal Repair of Esophageal Hiatus Hernia, S. Clin. North America **27**:109-116 (Feb.) 1947. Soutter, L.: Analysis of Cases of Hiatus Hernia Treated by Surgery at Massachusetts General Hospital, ibid. **27**:1121-1127 (Oct.) 1947. Harrington.[2a]

presence of tenderness and mild muscle guard in the epigastrium. Roentgenologic examination of the upper part of the gastrointestinal tract showed a small hiatus hernia to be present. The patient stated that this had been noted also on routine examination seven years previously but had never caused any symptoms. The diagnosis was asymptomatic hiatus hernia.

CASE 2.—S. D., a 48 year old white woman with moderate obesity, had been feeling well until the sudden onset of a severe pressure type of pain in the retrosternal area. This came on while she was eating a steak dinner hurriedly during

Fig. 2 (case 1).—Asymptomatic hiatus hernia. Roentgenologic study showed upper 4 cm. of cardia above diaphragm.

a period of increased nervous tension. Further attempts at eating or swallowing resulted in a feeling as though food were sticking in the lower part of the esophagus and regurgitation occurred. She became apprehensive and faint. She was taken to a hospital admitting room, where a tentative diagnosis of acute coronary thrombosis was made, but she declined to stay in this hospital. When seen at home by one of us (R. S. L.) about an hour later, she was still in some distress but the pain was much less severe than it had been initially. Meperidine (demerol®) hydrochloride, 100 mg., was given hypodermically and the distress was relieved so that the patient could sleep through the night. The following day a normal electro-

cardiogram was obtained. Two days later roentgenologic examination disclosed the presence of a shortened esophagus and a large hiatus hernia containing most of the cardia of the stomach. During the six months since this episode no similar symptoms have occurred. She has to be careful to eat smaller meals, to eat more slowly and to chew her food well. The diagnosis was hiatus hernia with acute symptoms simulating acute coronary thrombosis.

CASE 3.—N. F., a 50 year old housewife, first came under observation because of myasthenia gravis. This was well controlled by the oral administration of neostigmine (prostigmin®) bromide. Before and since the onset of the symptoms of

Fig. 3 (case 2).—Symptoms of acute coronary thrombosis were simulated by this hiatus hernia.

myasthenia she complained of intermittent pains in the upper abdomen and distress coming on after meals, aggravated by eating of coarse foods and also by lying down. The symptoms were much improved by using a soft bland diet, eating small meals, staying upright for at least two hours after eating and taking small doses of phenobarbital and belladonna. However, acute upper abdominal pain and distress associated with severe repeated hematemeses occurred on one occasion. It was necessary to use 8 pints (3.8 liters) of whole blood within a period of forty-eight hours to keep her out of shock. After the bleeding had stopped, roentgenologic

examination showed a small hiatus hernia with an apparent constriction at the junction of an esophagus and hernia. Three months later no hiatus hernia could be demonstrated. Seven months later, at a time that similar epigastric symptoms of pain, fulness and vomiting (but without evidence of bleeding) occurred, the small reducible hiatus hernia was again demonstrated by roentgenogram. No other abnormalities were observed in the gastrointestinal tract. The diagnosis was intermittent hiatus hernia with massive hematemesis.

CASE 4.—L. C., a 71 year old white man, was admitted to the University Hospital with complaints of "gas on stomach" and loss of 31 pounds (14.1 Kg.) in

Fig. 4 (case 3).—Severe hematemesis and melena resulted from this small hiatus hernia, not observed at previous examination.

weight during the preceding three months, vomiting of food soon after meals and passing of black tarry stools for three weeks and vomiting of blood for three days. Roentgenologic examination showed herniation of the upper third of the stomach through the esophageal hiatus with a neoplasm involving the herniated portion. At operation the hernial ring was found to be large enough to admit the hand. A biopsy specimen from the tumor area was reported to show sarcoma of the stomach. The diagnosis was hiatus hernia with sarcoma of the stomach in the herniated portion.

CASE 5.—W. C., a 33 year old white man, complained of epigastric distress radiating upward into the chest, occurring chiefly about one to two hours after

meals and somewhat relieved by taking alkali or further food. This symptom had been present for about five years. About nine years before his admission, while he was pitching hay, something seemed to "pop" in his right side, after which he had pains in the right lower portion of the chest. His condition was treated for two months as a case of pleural fluid or empyema. A thoracotomy was done at that time. About one year after this event, while carrying water, he felt a tearing sensation in the epigastrium and fell as though shot. Roentgenologic examination at the time of his admission to the University of Nebraska College of Medicine Dispensary showed herniation of the stomach and transverse colon through

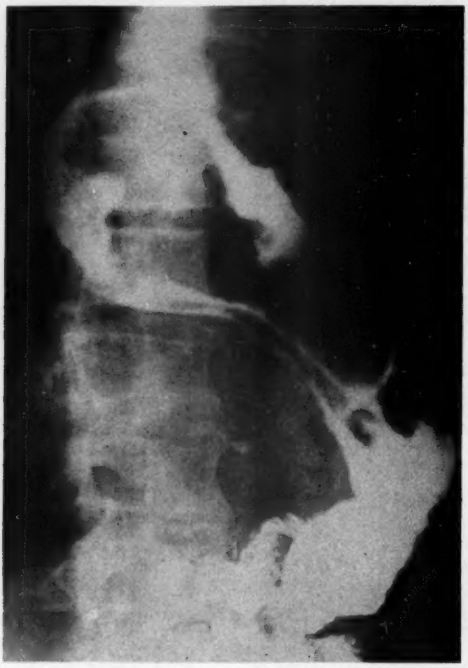

Fig. 5 (case 4).—Sarcoma of stomach occurring within large herniated gastric pouch.

the esophageal hiatus. The fundus of the stomach was at the level of the seventh rib posteriorly, and there was a fluid level in the right side of the chest at the level of the ninth rib posteriorly. The diagnosis was traumatic hiatus hernia of stomach and transverse colon.

Case 6.—M. J., a 22 year old Negro woman with a normal pregnancy, was admitted to the University Hospital about one month before term. She stated that a respiratory infection with severe coughing had begun three days previously. On the day of her admission vomiting had occurred some seven or eight times. On

three occasions the vomitus contained red blood. Emesis of "coffee-ground" material occurred several times after her admission to the hospital, and the patient complained of pain in the upper abdomen and distress which was largely relieved by vomiting. Fluids were given intravenously during the first twenty-four hours the patient was in the hospital, after which the symptoms gradually subsided. Roentgenologic examination showed a shortened esophagus, a large hiatus hernia and the stomach pushed up under the left side of the diaphragm by the enlarged uterus. The diagnosis was hiatus hernia occurring during the last trimester of pregnancy, with pain, vomiting and hematemesis following coughing.

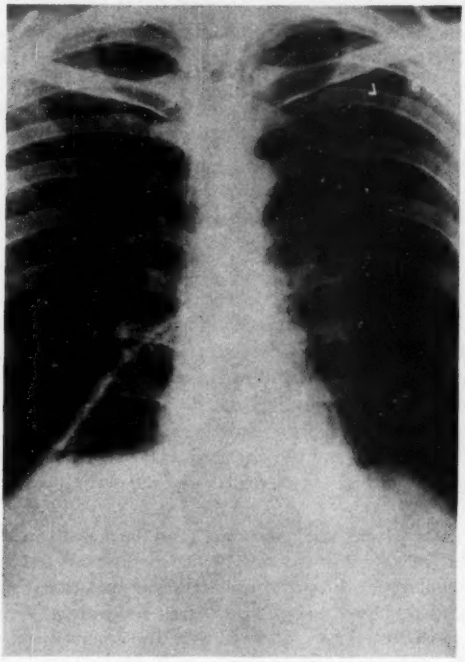

Fig. 6 (case 5).—Intrathoracic fluid level occurring within thoracic stomach herniated through large diaphragmatic hiatus.

COMMENT

Hiatus hernia is a fairly common condition which may be asymptomatic at the time it is discovered or may be the cause of serious symptoms and signs. We believe that it is dismissed too frequently from consideration in the differential diagnosis of various conditions occurring in the upper part of the abdomen and chest. Its presence should always be considered clinically significant, even though it does not prove

to be the cause of the disorder under investigation at the time. On the other hand, if symptoms and signs at a given time are shown to be due to hiatus hernia, one must be careful not to overlook later some other unrelated pathologic condition which may produce a similar clinical picture.

It is unfortunate that the symptoms of hiatus hernia may so closely resemble those of "nervous indigestion" or "functional dyspepsia." However, if the medical history is taken carefully and completely, the two can usually be differentiated and the diagnosis verified by careful roentgenologic examination. No doubt many patients are labeled as a "functional gastrointestinal problem" or as having "nervous indigestion" because of the occurrence of certain symptoms together with the presence of certain emotional problems, when in reality the principal somatic symptoms are due to the mechanical disability incident to the hiatus hernia. If certain symptoms can be attributed properly to the hernia and if the manner of their production is explained to the patient, together with appropriate advice on their management, he will almost invariably be considerably relieved from his anxiety about the symptoms and will accept gracefully and gratefully the advice given. The emotional problems can then be dealt with on their proper plane. The physician is then in a much more advantageous position to help the patient than if he had overlooked the possibility that a part, or all, of the somatic symptoms were due to some mechanical disorder. Much time may be wasted in analyzing and rationalizing emotional problems in such a fashion as to explain somatic symptoms which are in reality of a mechanical nature, and the physician may place too much emphasis on emotional problems which really are not seriously bothering the patient.

On the other hand, the physician must be equally careful not to allow the finding of a hiatus hernia which is probably not symptomatic to distract him from a proper consideration of and attention to important emotional problems. Here again is an illustration of the fact that the patient must always be considered as a whole person and the emphasis properly distributed to the various "organic" and "functional" aspects of the particular case.

SUMMARY

Acute symptoms due to hiatus hernia may simulate acute coronary heart disease. Chronic symptoms due to hiatus hernia may simulate chronic heart disease. Massive or moderate hematemesis and/or melena may be due to hiatus hernia. Peptic ulcer in the stomach or duodenum may be associated with hiatus hernia. A malignant neoplasm may develop in or near the herniated portion of the stomach and produce

symptoms and signs similar to those of the hiatus hernia alone. Trauma, such as coughing or straining, may produce a hiatus hernia or cause symptoms to arise from such a hernia which previously has been asymptomatic.

Hiatus hernia may be present without producing symptoms but should always be considered clinically significant, as it may become symptomatic at any time. The finding of a hiatus hernia or knowledge of its presence should not deter the clinician or roentgenologist from searching carefully for other pathologic changes which might produce similar symptoms or signs.

Fluoroscopy and roentgenography of the stomach should always include a careful search for hiatus hernia. This necessitates examination with the patient in the supine head-down position at some time during the fluoroscopy. Repeated examinations may be necessary to demonstrate the hernia.

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CHANGING PATHOGENESIS OF ADDISON'S DISEASE

With Special Reference to Amyloidosis

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THE DISTURBANCES in electrolytic equilibrium, in water balance and in the metabolism of carbohydrates and pigments which are observed in Addison's disease are known to reflect adrenocortical hypofunction. This, in turn, is dependent on severe retrogressive changes in the adrenal glands, often terminating in extensive bilateral destruction. Various etiologic processes have been incriminated in the production of the structural alterations.

Review of 2,550 autopsy protocols by Philpott [1] in 1928 (University Hospital, Ann Arbor, Mich.) disclosed 14 cases with morphologic features providing a basis for chronic adrenal insufficiency. In 7 the lesions were due to tuberculosis and in 4 to metastatic carcinoma. Of the remaining 3 cases, 1 was ascribed to mycosis fungoides, 1 to simple atrophy and 1 to amyloidosis. Today, twenty-two years later, it seems worth while to study the subsequent 9,000 postmortem records to determine whether the same etiologic factors are operative and, if so, to learn whether there have been changes in their relative competitive frequency. The analysis of a complete series covering this period should test the validity of the presumption that selective cortical necrosis of the adrenal glands is on the increase.

In selecting cases for this study, rigid criteria were employed and only those cases adequately demonstrating both clinical and pathologic features were included. In each case so accepted there had been asthenia, dizziness and fatigue. All patients had had gastrointestinal symptoms, anorexia, nausea and vomiting, and some had had diarrhea. They all had been hypotensive and had shown a loss of weight; some had had decreased tolerance to cold, and a few died in a state of terminal circulatory collapse. A progressive cutaneous brown pigmentation was seen in each patient except one, varying only in degree of intensity and in distribution. It was usually present on exposed surfaces, such as the hands and face, but was also recognized on the

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1. Philpott, N. W.: Addison's Disease in Association with Amyloidosis, Ann. Int. Med. **1**:613 (Feb.) 1928.

areola of the nipples, axillary folds, abdomen, buttocks, genitalia, umbilicus and oral mucous membranes. Occasionally the first manifestation of disturbance in pigment metabolism was in an old scar.

In the 9,000 necropsy records since 1929, 18 additional instances of Addison's disease were found which met these strict criteria. The clinical and pathologic changes in these cases will be discussed, with special emphasis on the morphologic alterations and on the clinical features of age, sex and duration of symptoms in the subgroups due to tuberculosis, cytotoxic cortical necrosis and amyloidosis.

Cytotoxic cortical necrosis seemed to be the most appropriate designation for the morphologic features observed in the adrenal glands in the second category. Since the significant retrogressive change is necrosis of cortical cells, this term describes the pathologic process accurately. In the literature this condition is also known as primary atrophy, idiopathic atrophy or selective cortical necrosis. It is recognized that no toxic agent has been proved and that death of cortical cells may be due to progressive anoxia rather than to an extracellular poison.

TUBERCULOSIS

Tuberculosis has long held the leading role in the pathogenesis of this syndrome. Guttman [2] (1930) reviewed the available cases of Addison's disease from 1900 to 1929. Among 403 cases with postmortem studies he noted that about 70 per cent were due to tuberculosis, while 16 per cent were ascribed to primary atrophy.

In the present series derived from 9,000 necropsies, advanced bilateral tuberculous adrenalitis was the underlying process in 8 of 18 patients. Thus, tuberculosis was observed to play a less frequent role than Guttman's [2] figures indicated.

Five of the 8 patients were male. In age, the range was from 17 to 45 years. The development of the adrenal lesion was usually a complication of tuberculosis elsewhere. In 4 patients there was evidence of old healed pulmonary tuberculosis, and in 2 there was advanced active pulmonary tuberculosis with cavitation. In 1 patient the older lesion was chronic caseous tuberculous osteomyelitis of the second and third lumbar vertebrae and in the last patient no other tuberculous focus was seen. After the onset of endocrinopathic symptoms, the average length of survival was approximately one year.

Macroscopically, the adrenal glands of 6 patients were enlarged to twice or three times the normal size. The resulting pattern was dependent on the extent of caseous necrosis and reactive proliferation. In most glands there was prominent necrosis with a central yellowish

2. Guttman, P. H.: Addison's Disease: A Statistical Analysis of 566 Cases and a Study of the Pathology, Arch. Path. **10**:742 (Nov.); 895 (Dec.) 1930.

caseous mass surrounded by a rim of fibrous connective tissue; however, in a few of the adrenal glands the tuberculous process consisted of multiple confluent nodules with moderate necrosis. In each gland the medulla was not recognizable and it was difficult to identify any surviving cortical tissue with the naked eye. In the 2 remaining patients the adrenal glands appeared as white fibrous cords with included flecks of lime salts running through adipose tissue.

Histopathologically, there was widespread destruction of the adrenal glands with replacement, for the greater part, by tuberculous

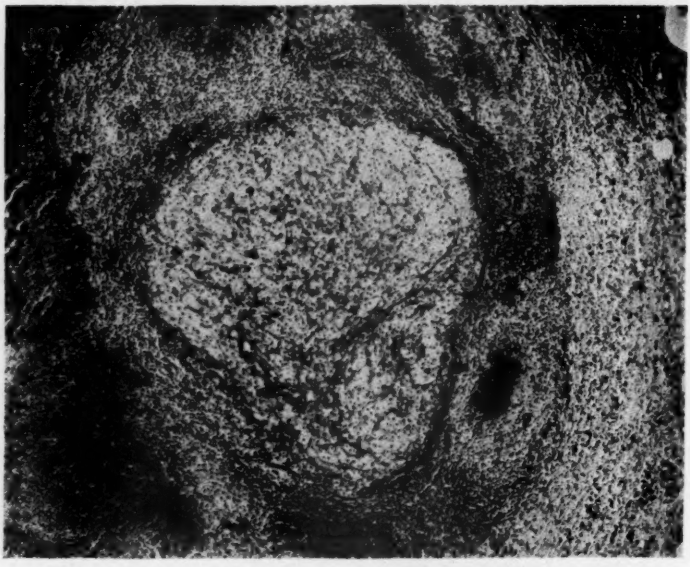

Fig. 1.—Tuberculosis of the adrenal gland, producing clinical Addison's disease. Tuberculous granulation tissue surrounds a nodule of surviving hyperplastic cortical cells. There is a young caseating epithelioid tubercle in the lower right portion of the field. Hematoxylin and eosin; × 50.

granulation tissue. In none of the material did medullary cells persist, and when cortical cells survived they were found as isolated groups of hypertrophic units in young proliferating connective tissue. Most of the surviving cortical cells had hyperchromatic nuclei, and the cytoplasm frequently appeared vacuolated. Corresponding to the medullary region were large areas of old caseous necrotic material with foci of dystrophic calcification and a peripheral zone containing areas of active caseation. Usually the productive reaction was extensive and the

resulting granulation tissue surrounded the necrotic material. This granulation tissue was composed of fibroblasts, connective tissue rich in collagen, cellular exudate of protracted inflammation, Langhans' giant cells and satellite epithelioid tubercles showing early caseation. In 2 patients the pathologic process appeared much older and the adrenal glands were replaced by dense hyalinized connective tissue which contained calcific masses. Even in these glands, young caseating epithelioid tubercles were seen.

From the histopathologic observations the inflammatory process seemed to be one of prolonged progressive destruction, which is in accord with the chronicity of the clinical course. In each patient there was abundant evidence of continued activity of the tuberculous process with the production of young tubercles.

CYTOTOXIC CORTICAL NECROSIS

Cytotoxic necrosis of the adrenal cortex ranks second among the causes of Addison's disease. The first mention of this process, according to Rowntree and Snell,[3] was by Addison in the original description of the disease which bears his name. By 1885 Coupland [4] was able to review 6 cases in which cortical necrosis produced adrenal hypofunction. As mentioned, Guttman [2] ascribed cortical destruction to atrophic changes in 16 per cent of a large series of patients. In 1933 Susman [5] discussed the experiences of the English with this disease and considered cortical necrosis to be responsible for about 35 per cent of the cases. He was of the opinion that this form is commoner in his country than elsewhere. In 1937 Wells and his colleagues [6] stated that the frequency of selective cortical necrosis was increasing and postulated a theoretic toxic substance as the cause. Mason,[7] in 1940, stated his view that cytotoxic necrosis was responsible for at least 50 per cent of the cases and had displaced tuberculosis to rank second among the causes of destructive lesions of the adrenal glands. In the current autopsy series it was observed that cytotoxic cortical necrosis accounted for about one third of the cases of Addison's disease. Although a slight absolute increase in the incidence of this

3. Rowntree, L. G., and Snell, A. N.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

4. Coupland, S.: Atrophy of Adrenals with Addison's Disease, Tr. Path. Soc. London **36**:423 (Feb.) 1885.

5. Susman, W.: Atrophy of the Adrenals Associated with Addison's Disease, J. Path. & Bact. **33**:749 (July) 1930.

6. Wells, H. G.; Humphreys, E. M., and Work, E. G.: Significance of the Increased Frequency of Selective Cortical Necrosis of Adrenal as a Cause of Addison's Disease, J. A. M. A. **109**:490 (Aug. 14) 1937.

7. Mason, E. H.: Diseases of the Ductless Glands, in Meakins, J. C.: The Practice of Medicine, ed. 3, St. Louis, C. V. Mosby Company, 1940, p. 895.

entity occurred in the last 9,000 autopsies, its remarkable percentage rise is explained to a greater degree by the reduced frequency of tuberculosis as a cause of Addison's disease. Moreover, the tendency of pathologists to report this interesting and unusual type may account for its prominence in the literature. Duff and Bernstein [8] in 1933 further attributed the increased incidence of this morphologic change to the then current reports of cases which had been collected from earlier autopsy records extending over long periods.

Although speculation has been stimulated in regard to the pathogenesis of cortical necrosis, the cause has remained obscure. Theoretic cytotoxic agents of bacterial,[9] metabolic [10] or unknown origin [6] have been proposed. Rogoff [11] devised a series of experiments which involved producing subtotal ischemia of the adrenal glands. The method was essentially ligation of the vessels to the glands and examination of the remaining tissue after varying periods. Rogoff stated that the pathologic changes induced by this procedure were the same as those which characterize idiopathic atrophy in human Addison's disease.

In that portion of the autopsy material included in this study were 6 cases of Addison's disease due to selective cortical necrosis. The age of the patients varied from 27 months to 70 years, and the average duration of symptoms was twenty-six months. Three of the patients were male. The clinical manifestations were those usually associated with Addison's disease, and there were no signs or symptoms which were peculiar to this group or accentuated in it. One of the patients was a 27 month old boy and his is thought to be the youngest recorded case with postmortem confirmation. Only 6 other instances [12] of Addison's disease have been described of children younger than 5 years and of these only 3 were proved by autopsy. The morphologic changes found in these cases were listed as cytotoxic cortical necrosis, tuberculosis and hyperplasia of the androgenic zone, one of each.

Case 1.—In the case seen at the University Hospital, Ann Arbor, Mich., the patient had been born prematurely at seven to eight months' gestation. The weight at birth was 4½ pounds (2,041 Gm.) Subsequently there was loss of

8. Duff, G. L., and Bernstein, C.: Five Cases of Addison's Disease with So-Called Atrophy of the Adrenal Cortex, Bull. Johns Hopkins Hosp. **52**:67 (Jan.) 1933.

9. Caldwell, G .T.: Atrophy of the Suprarenal Glands in Addison's Disease, Texas State J. Med. **27**:654 (Jan.) 1932.

10. Kovács, W.: Zur Nebennierenpathologie, Beitr. z. path. Anat. u. z. allg. Path. **79**:213 (Feb. 15) 1928.

11. Rogoff, J. M.: Experimental Pathology and Physiology of the Adrenal Cortex: Production of Addison's Disease in Laboratory Animals, Arch. Path. **38**:392 (Dec.) 1944.

12. Jaudon, J. C.: Addison's Disease in Children, J. Pediat. **28**:737 (June) 1946.

weight to 3½ pounds (1,588 Gm.) at 2 months. The mother stated that the child had a yellowish discoloration of the skin at birth which persisted. After the second month the gain in weight was progressive and the child weighed 18 pounds (8,165 Gm.) at the end of the first year. At 16 months there was an episode of coryza and at 20 months the patient had an ascaris infection. Thereafter he became constipated and received enemas. Anorexia developed during this period and continued. At 22 months the child began to stagger and frequently fell. He appeared weak and began to lose weight. At 24 months of age the child commenced to vomit and was hospitalized for a brief interval. Three months later, anorexia, vomiting and general weakness were severer.

At the time of his admission to this hospital, physical examination disclosed an extremely lethargic and listless boy with a peculiar yellowish brown pigmentation of the skin. He was much underweight for his age (19 pounds 3 ounces [8,702 Gm.]). There was an unusual streaking present on the peripheral portion of the retina of each eye, and small ulcerations of the mouth and gums were noted. The spleen was not palpable, but the border of the liver could be felt below the right costal margin.

Laboratory studies revealed the hemoglobin concentration to be 11.5 Gm. per hundred cubic centimeters of blood. Spinal puncture showed clear fluid with normal pressure and no cellular elements. The protein was 77 mg., sugar 78 mg. and the chlorides 108 mg., per hundred cubic centimeters. Therapy consisted of infusions of 10 per cent dextrose solution in distilled water and clyses of isotonic sodium chloride solution. The patient died about twenty-four hours after his admission, and the tentative clinical diagnosis was Addison's disease. At necropsy this impression was confirmed, for each adrenal gland consisted in the gross of only a grayish medulla, and microscopically the few remaining areas of cortical cells showed degeneration and necrosis. In addition, the pathologic diagnoses included melanoderma; generalized lymphoid hyperplasia except for fibrous atrophy of the thymus; localized lipidic pneumonitis; pulmonary and cerebral edema, and malnutrition.

The adrenal glands of the patients in this group were usually extremely small and altered in shape. They were flabby, grayish white and, in some instances, flat and ribbon-like in outline. In most cases the cortex was not visible and the capsule appeared to rest directly on medullary tissue. Adrenal substance was obtained in 1 patient only by preparing histologic sections of the perirenal adipose tissue and identifying it microscopically.

The histopathologic changes were those of a widespread and progressive cortical necrosis, best seen in the zona reticularis and zona fasciculata and, to a lesser degree, in the zona glomerulosa. For the greater part, the normal zonal and columnar arrangements of the cortex were lost but frequently a few cortical cells were observed beneath the capsule. The surviving parenchymal cells were pleomorphic; some resembled normal-appearing glomerulosa cells, but most were swollen and granular, with hyperchromatic nuclei and vacuolated to honeycombed cytoplasm. A few of the cells contained brown pigment, while others were in a late stage of necrosis. At different levels isolated nodular masses of cortical cells were seen between the capsule and

medulla. These areas, as well as nodular extracapsular hyperplastic cells, demonstrated the aforementioned changes. It appeared as though the supporting stroma of the cortex had collapsed with relative prominence of the connective tissue. In addition, there were extensive lymphocytic infiltrations, with the cells tending to be aggregated in clumps in both cortex and medulla. Medullary tissue was usually intact or involved to only a mild degree, and in a few instances the cells were smaller than normal. In every patient there was a notable reduction of lipids in the surviving cortical cells.

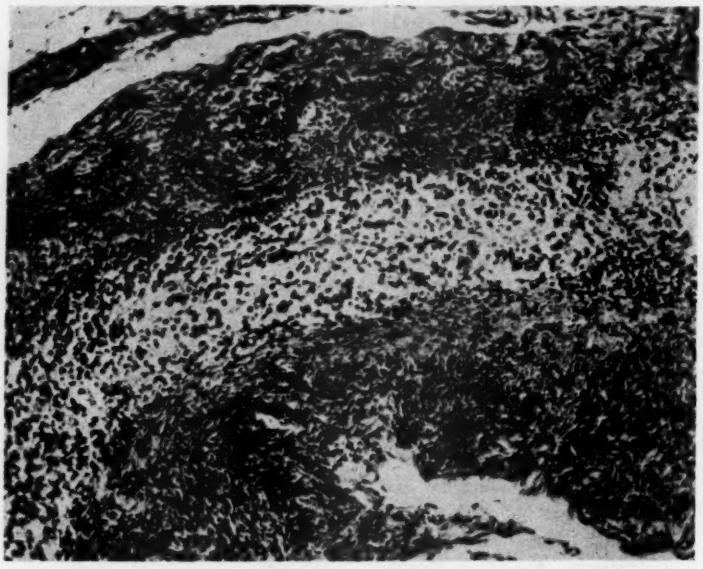

Fig. 2.—Cytotoxic (selective) cortical necrosis of the adrenal gland, producing clinical Addison's disease. The gland shows complete destruction of the cortex. The capsule rests directly on the medulla. Hematoxylin and eosin; × 160.

One patient in this group had bilateral miliary tuberculosis superimposed on the atrophic changes. Another had small foci of calcification in one adrenal gland.

AMYLOIDOSIS

Deposition of amyloid ranked third in frequency in this series as the cause of cortical insufficiency. Such deposits are of fairly common occurrence in the liver, kidneys, spleen and adrenal glands and usually are considered to be "secondary" to long-standing destructive diseases, such as tuberculosis and osteomyelitis. This form is in sharp distinction

from the "primary" or "atypical" variety in which amyloid infiltrates mesodermal derivatives and its deposition is not related to preexisting morbid states.

The histopathologic localization in secondary amyloidosis suggests that precursors of amyloid circulate in the blood and are removed by reticuloendothelial cells. This newly formed substance is usually laid down "behind" the reticuloendothelial cells in relation to the blood stream and is seen lying between the endothelial lining of sinusoids of the adrenal glands and the parenchymal cells. When the deposition is heavy, this dense resistant substance produces a pressure or starvation barrier which results in atrophy and eventual disappearance of tissue cells. In the late stages only the blood spaces, endothelium and amyloid are left. Examination of adrenal glands in which the deposition is minimal shows that amyloid is first deposited in the zona fasciculata, but in more advanced cases the zona reticularis is infiltrated and to a less degree the zona glomerulosa. In advanced stages the latter zone shows extensive involvement, but even then some peripheral cortical cells persist. In correlating the degree of deposition of amyloid with the impairment of function of various organs, it is recognized that the liver and adrenal glands have a more liberal factor of safety than do the kidneys.

Amyloid deposition is present in the adrenal glands in most instances of generalized amyloidosis; however, only rarely will this infiltration produce Addison's disease. In the present study of 29 patients with moderately to extremely advanced adrenal amyloidosis there were only 3 in whom adrenocortical hypofunction was evident clinically and who died of Addison's disease. Various explanations have been proposed for the comparative rarity of the addisonian syndrome in adrenal amyloidosis. Practically all are based on the incomplete destruction of cortical tissue as usually seen microscopically. Apparently most patients die before a critical level of adrenal destruction has been reached, either from the predisposing disease itself (tuberculosis, osteomyelitis) or from renal insufficiency on the basis of nephropathia amyloidea. Eleven of these patients with generalized secondary amyloidosis died of renal failure. In the primary form of amyloidosis cardiac failure has been observed frequently as a result of myocardial involvement.

Review of the literature yields about 15 reported cases of Addison's disease due to amyloidosis. The first report was in 1910 by Bittorf.[13]

13. Bittorf, A.: Beiträge zur Pathologie der Nebennieren, Deutsches Arch. f. klin. Med. **100**:116 (Aug.) 1910.

Since then Schultz,[14] Schlesinger,[15] Bauer,[16] McCutcheon,[17] Hunter and Rush,[18] Philpott [1] and Mendel and Saibil [19] have reported single cases. In 1935 Colton [20] added 2 more and Bronfin and Guttman [21] wrote of this condition in 5 patients. From the present material I am able to report on 3 patients (in addition to the earlier patient of Philpott [1]) in whom infiltration with amyloid produced destruction of cortical cells and the clinical manifestations of Addison's disease. Because of the rarity of this clinicopathologic association, brief accounts of these 3 persons are included.

Case 2.—The first patient was a 35 year old white woman who for four years had complained of dizziness and progressive weakness. In addition there was severe anorexia which became more pronounced terminally, as did also intolerance to cold. The patient was observed to be well developed and fairly well nourished. The thyroid gland was diffusely enlarged. A nontender palpable mass in the right upper abdominal quadrant was ascribed to hepatomegaly. The spleen likewise was palpable. Blood pressure was 108 systolic and 74 diastolic. Increased pigmentation of the areola of the nipples was noted. The plasma nonprotein nitrogen was 61.2 mg., and fasting blood sugar was 111 mg. per hundred cubic centimeters. Urinary specific gravity was 1.010, and there were many hyaline and granular casts and albuminuria (4 plus). The hemoglobin concentration ranged from 40 to 60 per cent.

This woman presented a diagnostic problem to the clinicians, and the prevailing impression was that of chronic nephritis with secondary anemia. The weakness continued until her death.

At necropsy both adrenal glands were seen to be enlarged and firm and the cortexes were nodular and translucent.

Pathologic diagnoses included Addison's disease from advanced adrenal amyloidosis; amyloid deposition in kidneys, liver, spleen, stomach, small intestine, lymph

14. Schultz, O. T.: Complete Amyloid Infiltration of Both Adrenals Associated with Addison's Disease, Cleveland M. J. **11**:40 (Jan.) 1912.

15. Schlesinger, H.: Subakute Insuffizienz der Nebennieren bei Amyloidose, nebst Bemerkungen über den Morbus Addisonii, Wien. klin. Wchnschr. **30**:99 (Jan. 25) 1917.

16. Bauer, J.: Paroxysmale schwerste Adynamie bei Amyloidose der Nebennierenrinde, Klin. Wchnschr. **1**:1595 (Aug.) 1922.

17. McCutcheon, M.: The Relation of Addison's Disease to Amyloidosis, Am. J. M. Sc. **166**:197 (Aug.) 1923.

18. Hunter, W. C., and Rush, H. P.: Amyloidosis of the Adrenals as a Cause of Addison's Disease: Report of Case with Review of the Literature, Ann. Clin. Med. **5**:404 (Oct.) 1926.

19. Mendel, D. L., and Saibil, M.: Amyloidosis of the Adrenals as a Cause of Addison's Disease, Canad. M. A. J. **39**:457 (Nov.) 1938.

20. Colton, W. A.: Tuberculosis as a Causative Factor in Addison's Disease: Report of Cases, M. Bull. Vet. Admin. **12**:27 (July) 1935.

21. Bronfin, I. D., and Guttman, P. H.: Amyloid Degeneration of the Adrenals as a Factor in Producing Symptoms of Addison's Disease in Chronic Pulmonary Tuberculosis, Am. Rev. Tuberc. **31**:1 (Jan.) 1935.

nodes, coronary vessels and endocardium; active chronic fibrocaseous pulmonary tuberculosis; ulcerating tuberculous enteritis and colitis; chronic purulent bronchitis and bronchiectasis, and ascites.

CASE 3.—The second patient was a 25 year old woman who, at the time of her admission, complained of weakness, abdominal pain and cramps and burning on urination. Other symptoms included loss of weight, ease of fatigue, nausea, vomiting and diarrhea. Illness was thought to be related to pulmonary tuberculosis, since five years previously the patient had been admitted to a sanitorium for tuberculous patients after an episode of hemoptysis and pleurisy. Treatment consisted of rest in bed, and eighteen months later the patient was discharged. Recently the tuberculosis was reactivated and the patient showed the symptoms mentioned previously. The weakness and loss of weight were extreme.

On examination this woman appeared to have lost much weight. Blood pressures were 90 systolic and 65 diastolic. There was tenderness in the right upper abdominal quadrant. Over the face and arms there were areas of brown pigmentation which recently had become more prominent.

Laboratory findings included albuminuria (3+), urinary specific gravity of 1.010 and many hyaline and granular casts. The hemoglobin concentration was 58 per cent and the nonprotein nitrogen was 28 mg. per hundred cubic centimeters.

On postmortem examination both adrenal glands were firm and cut with increased resistance.

Essential pathologic diagnoses were Addison's disease secondary to amyloid infiltration of adrenal glands; generalized amyloidosis, most pronounced in the spleen; bilateral pulmonary tuberculosis with cavitation, and ulcerating tuberculous enteritis and colitis.

CASE 4.—The last case was that of a 22 year old white man who gave a history of progressive fatigue, dyspnea and weakness of nine months' duration. About four months after the onset of these symptoms, swelling of the lower extremities developed. There had been a loss of weight of 15 pounds (6.8 Kg.). During several months numerous pinhead to pea-sized pigmented macules of varying depths of brownness and with irregular borders had appeared on the upper part of the back, arms and face. The patient was well developed and well nourished, alert and fully oriented. His blood pressure was 70 systolic and 50 diastolic. Other physical findings were cardiomegaly, pleural effusion and hepatomegaly. The hemoglobin concentration was 17 Gm., albumin 2.3 Gm. and globulin 2.1 Gm., per hundred cubic centimeters. The nonprotein nitrogen was 44 mg.

Histopathologic study of a cutaneous lesion revealed patchy melanoderma, with an increased number of chromatophores in the upper part of the corium. This change was considered compatible with Addison's disease, and the Addison's disease, in turn, was attributed to amyloid infiltration when a gingival specimen was noted to contain hyaline material which gave a positive stain for amyloid. This sequence was confirmed by autopsy.

Essential pathologic diagnoses were Addison's disease secondary to adrenal amyloidosis; primary amyloidosis involving liver, spleen, heart, lungs, larynx, kidneys, lymph nodes, bone marrow, skin and gastrointestinal tract, and anasarca.

These 3 patients had many morphologic features in common. The adrenal glands were enlarged, having a combined weight of 30 to 40 Gm. in each instance. Corticomedullary distinction was reduced, and the usual yellow-appearing cortex was replaced by firm, gray, translucent material.

Microscopically, amyloid was found deposited in the zonae reticularis and fasciculata and in practically all the zona glomerulosa, with correspondingly extensive loss of cortical elements. It also encroached on the medulla, with resultant reduction in the amount of chromaffin tissue. In each instance a portion of the zona glomerulosa survived as subcapsular islands of cells or in small nodular masses of extracapsular cortical hyperplasia. In general, each cortex was an eosinophilic hyaline mass containing patchy islands of dilated sinusoids and minimal parenchymal tissue.

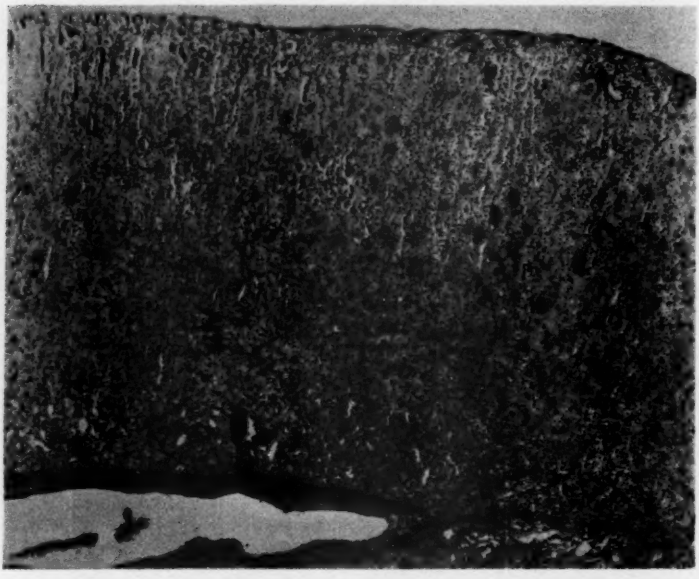

Fig. 3.—Amyloidosis of the adrenal gland, producing clinical Addison's disease. The cortex shows extensive infiltration by amyloid and loss of cortical cells. Some of the peripheral cells of the zona glomerulosa have survived. Hematoxylin and eosin; × 31.

HISTOPLASMOSIS

The remaining case of Addison's disease in this series was believed to be due to destruction of the adrenal cortex as part of a generalized histoplasmotic infection. This is listed as probable rather than proved. The histopathologic changes were those ascribed to this fungus, and intracellular organisms were seen, but confirmatory cultural studies were not performed.

Parsons and Zarafonetis [22] cited the case of a 63 year old white man who showed evidences of adrenal insufficiency toward the end of his illness and was treated with adrenal cortex extract. At autopsy there was bilateral adrenal necrosis due to histoplasmosis. Rawson, Collins and Grant [23] described a patient in whom the clinical findings were those of adrenal failure and of an associated infectious disease. Autopsy observations disclosed extensive necrosis of both adrenal glands due to histoplasmosis. Reference is made by these authors to 8 other cases (including the one cited by Parsons and Zarafonetis) in which adrenal insufficiency was related to this infection. The following case seems to be similar to these experiences.

CASE 5.—The patient was a 58 year old white man who was in apparent good health until three years previously, when he noticed small scattered papular and pruritic lesions over his arms and legs. When these were scratched, a crust would form and the lesions subsequently disappeared. At the time the patient was first seen, such papules were present.

Approximately three months prior to admission to the hospital the patient had a cough productive of yellow, blood-streaked sputum. In addition, there were dyspnea on exertion, fatigue, fever and night sweats. Anorexia was pronounced, and there was a history of a loss in weight of 35 pounds (15.9 Kg.) during this period. On physical examination the patient was seen to have numerous crusted red lesions over the thighs, legs and arms. There were palpable lymph nodes in the left axillary and inguinal regions. Dulness and bronchovesicular breathing were elicited over the right apex, while crackling inspiratory rales were heard at the bases of the lungs. Blood pressure was 98 systolic and 60 diastolic. The spleen was questionably palpable.

Laboratory findings included determination of the hemoglobin concentration as 14 Gm. per hundred cubic centimeters of blood, which later dropped to 12.5 Gm. Nonprotein nitrogen was 51 mg. per hundred cubic centimeters. A blood culture was negative for pathogens, and examination of the sputum failed to demonstrate acid-fast organisms. The tuberculin reaction was negative. Serum proteins were 9 Gm., albumin 2.8 Gm. and globulin 6.2 Gm., per hundred cubic centimeters. Roentgenologic examination disclosed an area of increased density and reticulation in the upper right pulmonary field, thought to be due to chronic interstitial pneumonitis.

The predominating clinical impression at this time was that the patient probably had sarcoidosis. The course in the hospital was one of downward progression. The patient failed to eat but vomited repeatedly. The blood pressure became lower, 70 systolic and 40 diastolic, and the heart action was weak. There were pain on swallowing and extreme fatigue and weakness. The patient died on the twenty-fifth day in the hospital.

At autopsy the adrenal glands were observed to be enlarged, with the left measuring 8.5 by 1.5 cm. and weighing 42 Gm. The right adrenal gland measured

22. Manchester, B.: Personal communication, cited by Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man: Report of 7 Cases and a Review of 71 Cases, Arch. Int. Med. **75**:1 (Jan.) 1945.

23. Rawson, A. J.; Collins, L. H., Jr., and Grant, J. L.: Histoplasmosis and Torulosis as Causes of Adrenal Insufficiency, Am. J. M. Sc. **215**:363 (April) 1948.

8 by 4 by 2 cm. and weighed 44 Gm. Both glands were firm and mottled pink to grayish yellow on the cut surface. A few hemorrhagic-appearing areas were seen, but no normal adrenal tissue was recognized.

Microscopic examination of the adrenal glands showed a massive, active caseation necrosis. No medullary cells remained, and only a few cortical elements were surviving beneath the capsule. The granulation tissue which rimmed the necrotic mass was composed of fibroblasts, collagen-rich connective tissue, plasma cells, lymphocytes and many newly formed blood vessels. In addition, there were abundant mononuclear phagocytes which contained round or oval bodies measuring 2 to 4 microns in diameter. Each body consisted of central chromatin material surrounded by clear cytoplasm. These yeastlike organisms were thought to be Histoplasma capsulatum.

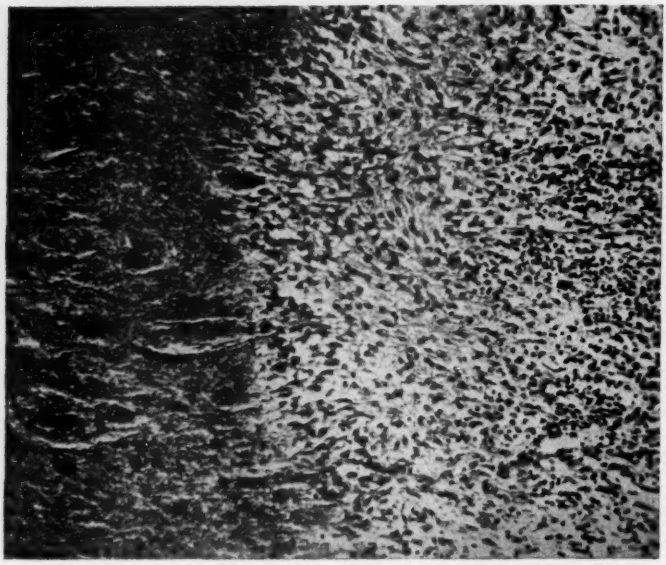

Fig. 4.—Histoplasmosis of the adrenal gland, producing clinical Addison's disease. The gland shows caseation necrosis and granulation tissue which is composed chiefly of epithelioid cells and lymphocytes. The causative organism is not seen at this magnification. Hematoxylin and eosin; × 160.

Stains for acid-fast organisms were applied to sections of most of the organs in which the chronic infective granulomatous change was observed without positive results. Furthermore, in none of the tissues, other than the adrenal gland, was H. capsulatum demonstrated.

Essential pathologic diagnoses included histoplasmosis; infective granulomatous caseous adrenalitis; Addison's disease; epithelioid nodules and more diffuse granulation tissue in lungs, paratracheal, mesenteric and retroperitoneal lymph nodes, spleen, liver, colon, kidneys and prostate; acute pustular and vesicular dermatitis, and acute purulent bronchitis and bronchopneumonia.

COMMENT AND SUMMARY

Philpott's [1] analysis of the first 2,550 autopsies at the University Hospital in respect to the etiologic basis of Addison's disease presents an interesting contrast when compared with the material indexed since 1929 (table). It is evident that there has been an absolute reduction in tuberculosis as a cause of Addison's disease. In this I agree with the impression gained by Thorn.[24] The change is apparently a part of the general reduction in tuberculosis, both medical and surgical, but credit must be given also to the more successful handling of tuberculous patients with respect to early diagnosis and more adequate treatment. It is probable that the true clinical incidence of Addison's disease has been reduced as compared with earlier years.

The cases of idiopathic cytotoxic necrosis and atrophy are too few to justify a positive conclusion other than that the increase appears to have been only moderate, if there has been any increase at all. In the future, the apparent increase in this form may appear more significant

Comparative Distribution in the Two Series of Autopsies of the Thirty-Two Cases of Addison's Disease According to Pathogenesis

	2,550 Autopsies (1895 to 1928)	9,000 Autopsies (1929 to 1949)
Tuberculosis	7	8
Atrophy (cytotoxic necrosis)	1	6
Amyloidosis	1	3
Metastatic carcinoma	4	0
Mycosis fungoides	1	0
Histoplasmosis	0	1 (probable)

than can be substantiated by the actual increase in numbers, because it is usually considered in comparison with tuberculous Addison's disease. The pathogenesis of selective cortical necrosis is still not established, but Rogoff's experiments [11] on subtotal vascular occlusion suggest that the adrenal vessels in human material should be searched for obturating changes. Lesions of this type might produce progressive infarction of the cortex. That cortical necrosis may produce Addison's disease in young children is substantiated from present necropsy material.

Amyloidosis is a rare cause of Addison's disease but now ranks third in this association. The so-called primary or atypical form, as well as secondary amyloidosis, may produce this syndrome.

Histoplasmosis should be added to the list of diseases capable of destroying adrenal parenchyma with the production of the clinical symptoms and signs characteristic of Addison's disease. It is probable that other systemic fungous infections will be found, on rare occasions, to play a causal role.

24. Thorn, G. W.: Diseases of the Adrenal Glands, in Cecil, R. L.: A Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Company, 1947.

LIPOPHAGIC INTESTINAL GRANULOMATOSIS (WHIPPLE'S DISEASE)

Clinical and Pathologic Study of Thirty-Four Cases, with Special Reference to Clinical Diagnosis and Pathogenesis

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RECENT literature contains increasingly frequent reports of lipophagic intestinal granulomatosis following generally the descriptive pattern of Whipple's first case in 1907, which he called intestinal lipodystrophy.

In this study of 34 collected cases the purpose is to establish the nature and frequency of the clinical features, in an attempt thereby to evolve a more clearcut pattern which may be of practical diagnostic value to the clinician. In addition, certain unusual pathologic characteristics, formerly considered coincidental, are now available in sufficient number to be significant. It will be indicated that these are indispensable in promoting a better understanding of pathogenesis and etiology. Also, a new case is presented, adding more data for analysis.

Clinically, this disease is characterized initially by polyarthritis and later by postprandial abdominal pain, distention, diarrhea, wasting and death. The anatomic changes are represented by lipogranulomas in the mucosa of the small intestine and mesenteric lymph nodes, as well as fibrous polyserositis.

SURVEY OF THE RECENT DOMESTIC LITERATURE AND CERTAIN FOREIGN CASES NOT REVIEWED IN THIS COUNTRY

Prior to 1947 there were only 18 cases of lipophagic intestinal granulomatosis known to various American authors.[1] Since that date

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10 new cases, including our own, have appeared.[2] The Rosens' review [2a] comprehensively covered the American literature to 1947 but apparently overlooked 6 existing foreign reports of cases fulfilling the criteria for

1. (*a*) Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, Bull. Johns Hopkins Hosp. **18**:382-391, 1907. (*b*) Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat, Arch. Int. Med. **32**:113-128 (July) 1923. (*c*) Fleischmann, R.: Ueber tumorbildende Fettgewebsgranulome im Gekröse des Dünndarms, Arch. f. klin. Chir. **158**:692-701, 1930. (*d*) Collins, A. N., and Berdez, G. L.: Chyle Cysts of Mesentery, Arch. Surg. **28**:335-344 (Feb.) 1934. (*e*) Jarcho, S.: Steatorrhoea with Unusual Lesions, Bull. Johns Hopkins Hosp. **59**:275-289 (Oct.) 1936. (*f*) Hill, J. M.: Mesenteric Chyladenectasis: Report of Case, Am. J. Path. **13**:267-276 (March) 1937. (*g*) Korsch, H. J.: Fettstoffwechselstörung mit Granulombildung in Mesenterium, Zentralbl. f. allg. Path. u. path. Anat. **71**:337-344 (Dec. 30) 1938. (*h*) Boeck, in discussion on Bargen, J. A.; Bollman, J. L., and Kepler, E. J.: Diarrhea of Pancreatic Insufficiency, Am. J. Digest. Dis. **4**:728-732 (Jan.) 1938. (*i*) Glynn, L. E., and Rosenheim, M. L.: Mesenteric Chyladenectasis with Steatorrhoea and Features of Addison's Disease, J. Path. & Bact. **47**:285-290 (Sept.) 1938. (*j*) Reinhart, H. L., and Wilson, S. J.: Malabsorption of Fat (Intestinal Lipodystrophy of Whipple): Report of Case, Am. J. Path. **15**:483-492 (July) 1939. (*k*) Sailer, S., and McGann, R. J.: Lipophagic Granulomatosis of Enteric Tract, Am. J. Digest. Dis. **9**:55-63, (Feb.) 1942. (*l*) Pearse, H. E.: Whipple's Disease, or Intestinal Lipodystrophy, Surgery **11**:906-911 (June) 1942. (*m*) Vaux, D. M.: Chyladenectasis with Steatorrhoea, J. Path. & Bact. **55**:93-96 (Jan.) 1943. (*n*) Apperly, F. L., and Copley, E. L.: Whipple's Disease (Lipophagia Granulomatosis), Gastroenterology **1**:461-470 (May) 1943. (*o*) Fitzgerald, P. J., and Kinney, T. D.: Intestinal Lipodystrophy (Whipple's Disease), Am. J. Path. **21**:1069-1089 (Nov.) 1945. (*p*) Amsterdam, H. J., and Grayzel, D. M.: Intestinal Lipodystrophy (Lipophagia Granulomatosis or Whipple's Disease), Am. J. M. Sc. **210**:605-611 (Nov.) 1945.

2. (*a*) Rosen, M. S., and Rosen, S. H.: Intestinal Lipodystrophy of Whipple: Report of Case and Analysis of Literature, Am. J. Path. **23**:443-461 (May) 1947. (*b*) Oliver-Pascual, E.; Galan, J.; Oliver-Pascual, A., and Castillo, E.: Un caso de lipodistrofia intestinal con lesiones ganglionares mesentéricas de granulomatosis lipofágia (enfermedad de Whipple), Rev. españ. enferm. ap. digest. y nutrición **6**:213-226 (May-June) 1947. (*c*) Frei, R.: Ueber die histopathologischen Veränderungen am Dünndarm bei Störungen der Fettresorption (sog. Xanthomatose des Dünndarms), Schweiz. Ztschr. f. Path. u. Bakt. **10**:685-702, 1947. (*d*) Pemberton, J. de J.; Comfort, N. W.; Fair, E., and Zaslow, J.: Intestinal Lipodystrophy (Whipple's Disease): Preliminary Report of 3 Cases in Early Stage of Disease, Surg., Gynec. & Obst. **85**:85-91 (July) 1947. (*e*) Newman, B., and Pope, R. H.: A Case of Intestinal Lipodystrophy (Whipple's Disease) Simulating Boeck's Sarcoid, Gastroenterology **11**:120-126 (July) 1948. (*f*) Chapnick, H. A.: Idiopathic Steatorrhea, with Report of a Case of Whipple's Disease: Case Report, Ann. Int. Med. **29**:549-558 (Sept.) 1948. (*g*) Rutishauser, E.; Demole, M., and Mach, R. S.: Sprue Due to Intestinal Lipostasis (Intestinal Lipodystrophy: Whipple's Disease), Rev. méd. Suisse rom. **68**:573-580 (Sept.) 1948.

this disease.[3] Those omitted were the Scandinavian case of Clemmesen (1945),[3d] the German cases of Fahr (1928),[3a] Gaertner (1938),[3b] Jeckeln (1939)[3d] and Kloos (1939)[3e] and the Argentine case of Escudero and his associates (1945).[3f] The 1947 report of Oliver-Pascual and his co-workers,[2b] plus the reports of Frei (1947)[2c] and Rutishauser and collaborators (1948)[2g] in Switzerland, apparently brings the recorded foreign cases up to date (table 1). All the aforementioned cases

TABLE 1.—*Reported Cases of Lipophagic Intestinal Granulomatosis (1907-1948)*

Year	No. of Cases Reported in the Year	Author	Nomenclature
1907	1	Whipple [1a]	Intestinal lipodystrophy
1923	3	Blumgart [1b] (3 cases)	
1928	1	Fahr [3a] *	
1930	1	Fleischmann [1c]	
1934	1	Collins & Berdey [1d]	
1936	2	Jarcho [1e]	
		Hill [1f]	Mesenteric chyladenectasis
1938	4	Korsch [1g]	
		Boeck [1h]	
		Glynn & Rosenheim [1i]	
		Gaertner [3b] *	
1939	3	Jeckeln [3d] *	
		Reinhart & Wilson [1j]	
		Kloos [3e] *	
1942	2	Saller & McGann [1k]	Lipophagic granulomatosis
		Pearse [1l]	
1943	2	Apperly & Copley [1n]	
		Vaux [1m]	
1945	4	Escudero et al.[3f]	
		Clemmesen [3g] *	Steatorrhea arthro-pericarditica
		Fitzgerald & Kinney [1a]	
		Amsterdam & Grayzel [1k]	
1947	6	Rosen & Rosen [2a]	
		Pemberton et al.[2d] (3 cases)	
		Oliver-Pascual et al.[2b]	
		Frei [2c]	
1948	3	Newman & Pope [2e]	
		Chapnick [2f]	
		Rutishauser et al.[2g]	
Total	33		

* Not included in former American reviews.

3. (*a*) Fahr, T.: Zur Frage des Zusammenhanges zwischen Stoffwechselstörungen und morphologischen Veränderungen im Reticuloendothelialen System, Klin. Wchnschr. **7**:1787-1791 (Sept. 16) 1928. (*b*) Gaertner, K.: Ueber einen Fall von hochgradiger Fettspeicherung in den Mesenteriallymphknoten, Frankfurt. Ztschr. f. Path. **52**:529-537, 1938. (*c*) Hansen, K., and von Staa, H.: Die einheimische Sprue und ihre Folgekrankeiten (sekundäre Avitaminosen), Leipzig, G. Thieme, 1936, p. 39; cited by Clemmesen.[3g] (*d*) Jeckeln, E.: Zur Pathologie der einheimischen Sprue, Virchows Arch. f. path. Anat. **303**:393-405, 1939. (*e*) Kloos, K.: Ueber eine eigenartige Fettresorptionsstörung und ihre Beziehung zur Sprue, ibid. **304**:625-658, 1939. (*f*) Escudero, P.; Mosto, D., and Landabure, P. B.: Lipodistrofia intestinal de Whipple, Arch. Soc. argent de anat. norm. y pat. **7**:139-163, 1945. (*g*) Clemmesen, J.: Steatorrhoea Arthro-Pericarditica (Mesenteric Chyladenectasis): Review and Report of Case, Acta med. Scandinav. **121**:495-524, 1945.

seem to be unfamiliar to American authors concerned with this disease and provide an unexpected substantial increase in the total number of cases available for study.

Clemmesen [3g] in 1945 collected the cases of Fahr, Gaertner, Jeckeln and Kloos, abstracted them and furnished 1 case of his own, thereby leading us to the original reports. Jeckeln's [3d] patient had been previously reported on (1936) during life as one with nontropical sprue (Hansen and von Staa [3c]), but the full clinical course and pathologic observations at autopsy appeared three years later with Jeckeln's report. Frei's [2c] case 2 fulfils even the more rigid criteria proposed by the Rosens and was described as an unusual case of xanthomatous deposits in the jejunum, along with another (case 1) that in no sense fulfils the usual criteria of this disease, clinically or pathologically. Eight American cases [4] have been recorded since 1945 and ours will make the ninth, bringing the total to 34. Rather than discuss each of these recently collected cases, we have tabulated their individual features in tables 2, 3 and 4.

This increase in incidence implies wider recognition or awareness of the disorder, especially by the pathologist, which can be appreciated when it is realized that a clinical diagnosis has been exceedingly rare in this group. Presumably, the incidence is greater than the listing in table 1 indicates, since some of the foreign cases were found published as descriptions of an obscure or previously unknown disorder of fat absorption.[5] The nomenclature applied by various authors appears in table 1.

A few of these 34 cases [6] have been excluded by certain authors because of various inconsistencies with other reports, but they are accepted by the majority [7] as conforming sufficiently, clinically and pathologically, to be included here. We have gained the impression that these differences represent only variations in duration of the disease and the degree of visceral involvement. In most respects, our case conformed to the general pattern and is reported as the thirty-fourth case.

REPORT OF A CASE

J. W., a 50 year old white man, was first seen (by W. H. H.) at the McGuire Clinic on Dec. 7, 1948. After two weeks' study and treatment, he was referred to McGuire Veterans Administration Hospital, on December 21. He presented the picture of a chronically ill, extremely cachectic, bedridden man, with a peculiar "muddy," sallow gray complexion.

He gave a history of weakness with anorexia and ill defined, diffuse, postprandial abdominal distress and distention, accompanied with a progressive loss of weight

4. Footnotes 1 *o* and *p* and 2 *a* and *d* to *f*.
5. Footnotes 3 *a*, *b*, *d* and *e* and 2 *c*.
6. Footnote 1 *b*, *c*, *d*, *h* and *l*.
7. Footnotes 1 *k*, *n* and *p* and 2 *d* and *e*.

TABLE 2.—*History and Symptoms in Thirty-Four Cases**

Case No.	Author	Sex	Age, Yr.	Duration, Yr.	History of Arthritis, Yr.	Gastrointestinal Symptoms: Pain and Distention	Gastrointestinal Symptoms: Constipation	Gastrointestinal Symptoms: Diarrhea	Weight Loss, Lb.	Prior Laparotomy	Other Significant Observations	Pathologic Diagnosis
1	Whipple [1a]	M	36	5½	5	0	.....	1 yr.	Mod. (30)	Terminal	Chronic productive cough	A
2	Blumgart,[1b] case 1	M	42	2	0	+	.....	4 mo.	Mild	4 mo.; appendicitis	Edema and indolent leg ulcers	A
3	Blumgart, case 2	F	44	2	+	0	+	+	Sev. (55)	0	.....	A
4	Blumgart, case 3	M	32	1½	0	0	.....	16 mo.	Sev. (85)	1 yr.	.....	A
5	Fahr [1a]	M	44	6	+	..	.....	6 mo.	+	.....	Chronic productive cough	A
6	Fleischmann [1c]	M	38	1	+	+	.....	+	+	Terminal	X-ray therapy; death in 2 mo.	A
7	Collins,[1d] case 2	F	48	½	..	+	.....	5 mo.	.....	Terminal	.....	A abd.
8	Jarcho [1e]	M	37	15	15	+	.....	2 yr.	Moderate	+	Jaundice 2 yr. before death	A
9	Hill [1f]	M	60	1	..	+	.....	1 yr.	Severe	0	.....	A
10	Korsch [1g]	M	60	10	10	+	.....	+	Sl. (20)	.....	.....	A
11	Boeck [1h]	M	45	1	..	..	.....	+	Sl. (25)	5 mo.	X-ray therapy; slight benefit	A
12	Glynn [1i]	M	44	1	..	+	6 mo.	+	+	+	.....	A
13	Gaertner [1b]	M	32	4	4	+	.....	1 yr.	Sev. (61)	.....	.....	A
14	Hansen [1c], Jeckeln [1d]	M	55	6	6	4 yr.	.....	4 yr.	+	.....	.....	A
15	Reinhart [1j]	M	74	1	0	+	1 yr.	0	Mod. (40)	.....	.....	A abd.
16	Kloos [1e]	M	41	5	5	+	.....	?	+	.....	Chronic cough	A
17	Sailer [1k]	M	45	5	5	+	+	0	Sl. (20)	0	? Onset of hematuria; chronic cough	A
18	Pearse [1l]	M	?	2	..	+	.....	+	.....	Repeated illness	Bile salts prescribed	Lap.
19	Apperly [1a]	M	51	4	3	+	.....	+	Mod. (45)	2 yr.	Lap. diagnosis, Hodgkin's disease	A
20	Vaux [1m]	M	49	9	9	+	.....	+	+	+	Prior gastrectomy; ? lesion	A
21	Amsterdam [1g]	M	54	2	0	+	.....	+	+	2 yr.	? Healed ileitis or tubere. at lap.	A
22	Fitzgerald [1a]	M	48	1	0	+	.....	1 mo.	+	+	Hemolytic anemia; splenectomy, chr. cough, periodic chest pain	A
23	Clemmesen [2a]	M	27	12	12	+	6 mo.	+	+	0	Hematuria 8 yr. after onset	A
24	Escudero [2b]	M	27	(?) 8	8	+	.....	3 mo.	Sev. (80)	0	Gonorrhea, polyarthritis and blennorrhagia at age 19; recurrence at 27	A
25	Oliver-Pascual [2b]	F	34	16	0	+	.....	16 yr.	Mod. (32)	Repeated illness	Worse during pregnancy; x-rays prescribed	Lap.†
26	Rosen [2a]	F	54	6 mo.	..	+	+	3 mo.	Sl. (15)	0	.....	A
27	Pemberton,[2d] case 1	M	60	3 mo.	?age 16	+	.....	3 mo.	Mod. (30)	Repeated illness	X-ray therapy prescribed	Lap.
28	Pemberton, case 2	F	62	1	..	0	.....	1 yr.	.....	Repeated illness	Bile salts prescribed; previous g. b. dis.	Lap.
29	Pemberton, case 3	F	58	?	?	+	0	+	0	Repeated illness	"Loose mucous stools"; x-ray therapy pres.	Lap.
30	Frei [2c]	M	43	5	5	+	.....	7 mo.	+	0	Tinsmith; chr. prod. cough	A
31	Newman [2e]	M	50	2	..	+	+	2 yr.	Sev. (95)	1 yr.	Lap. diagnosis, Boeck's sarcoidosis	A
32	Chapnick [2b]	M	37	1	0	+	+	+	+	0	.....	A
33	Rutishauser [2g]	?	?	?	+	..	.....	.....	+	.....	Swelling along tendons	A
34	Plummer	M	50	1	0	+	.....	2 mo.	Sev. (50)	0	Chronic productive cough	A

* Explanation of symbols: +, present; 0, absent; A, complete autopsy; A abd., autopsy confined to the abdomen; Lap., biopsy at laparotomy; mod., moderate; sev., severe; sl., slight; chr., chronic; prod., productive.

† The patient died, and autopsy was not performed

TABLE 3.—*Physical Findings in Thirty-Four Reported Cases* *

Case No.	Edema	Fever	Generalized Lymphadenopathy	Purpura	Pigmentation	Hypotension	Emaciation	Abdomen		Other	Symptoms Preceding "Sudden" Death
								Mass	"Doughy"		
1	+	0	+	+	"Pinhead"	+	+	Right lower quadrant	+	Arthritis	Dyspnea; cyanosis
2	+	0	..	+	+	+	+	..	..	.....	Dyspnea; aphasia
3	+	0	..	+	0	0	++	..	..	Glossitis; tetany	.....
4	0	0	..	0	0	+	++	..	+ Peristalsis	Tetany	Numbnss of extremities; dyspnea
5	..	0	..	..	..	+	+	+	..	.....	.....
6	..	..	..	..	..	..	+	+	..	.....	.....
7	..	..	..	..	..	..	+	Left lower quadrant	..	.....	.....
8	..	+	+	+	+	+	+	..	..	.....	.....
9	..	0	..	..	..	+	++	..	..	Marked somnolence	.....
10	..	..	..	..	..	..	+	Left upper quadrant	..	.....	.....
11	..	..	..	..	..	..	+	..	..	.....	.....
12	..	..	..	+	+	..	..	..	..	.....	.....
13	..	0	+	+	+	+	+	+	..	.....	+
14	+	0	..	+	..	+	+	..	..	.....	.....
15	+	0	+	+	0	+	++	Liver; spleen		Portal cirrhosis; ascites	Cyanosis; collapse
16	+	+	..	+	+	+	+	..	..	.....	.....
17	+	..	+	..	Yellow bronze	+	+	0	0	Ankylosis of ankles	.....
18	..	..	..	..	..	..	..	..	..	Distention	.....
19	+	..	+	+	+	+	+	..	..	.....	Chest pain; cyanosis
20	..	0	+	..	+	+	+	..	..	.....	.....
21	+	+	+	..	+	+	+	0	.. —	.....	.....
22	+	..	+	+	Jaundice	+	..	Spleen		Splenomegaly; arthritis	+
23	+	0	+	+	..	..	+	..	..	Bronchopneumonia	Mental confusion
24	0	+	..	+	+	+	++	0	0	Glossitis	.....
25	..	0	..	+	+	+	+	+, Midabdominal		Glossitis	.....
26	+	0	+	+	"Muddy"	+	..	Spleen		Splenomegaly	Vomiting; collapse
27	..	0	..	..	..	..	++	Epigastric		.....	.....
28	..	0	..	..	..	0	0	Midabdominal		.....	.....
29	..	0	..	..	..	..	0	Epigastric		.....	.....
30	0	0	..	+	+	+	+	..	0	.....	.....
31	+	0	+	+	+	+	+	0	+	Tetany	+
32	..	+	+	+	+	+	+	0	0	.....	.....
33	..	+	..	..	..	..	++	0	..	.....	.....
34	0	0	+	+	+	+	+	0	+	.....	Somnolence

* For key to abbreviations and authors, see table 2.

TABLE 4.—*Laboratory Data**

Case No.	Secondary Anemia	Achlorhydria	Fecal Fat	Blood Lipid	Nonprotein Nitrogen	Serum Protein	Calcium	Prothrombin Time	Blood Glucose	Other	Roentgenography: Small Bowel	Roentgenography: Other
1	+	..	Increased (neutral)	.....	.....	.....	.....	.....	.....	Eosinophilia	.....	Rheumatoid arthritis
2	+	+	Increased (fatty acid)	Normal	.....	.....	.....	.....	Low	.....	.....	.....
3	..	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
4	+	+	Normal	.....	.....	.....	Decreased	.....	.....	Duodenal enzyme normal	Normal	.....
5	+	..	.....	.....	.....	.....	.....	.....	.....	Positive Wassermann reaction	.....	.....
6	+	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
7	+	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
8	+	0	.....	.....	Increased	.....	.....	.....	Increased tolerance	.....	Normal	.....
9	+	..	.....	.....	.....	.....	.....	.....	Low	.....	.....	.....
10	..	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
11	+	+	Increased	.....	.....	.....	.....	.....	.....	.....	Deficiency pattern	Osteoporosis
12	..	0	Increased (fatty acid)	.....	.....	.....	.....	.....	.....	.....	.....	.....
13	+	+	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
14	+	+	Increased	.....	.....	.....	.....	.....	.....	.....	.....	.....
15	+	+	.....	.....	Decreased	.....	.....	.....	.....	.....	.....	.....
16	+	+	.....	.....	Increased	Normal	.....	.....	Normal	.....	.....	.....
17	+	+	.....	.....	Increased	Decreased albumin	.....	.....	Increased tolerance	.....	Deficiency pattern	Rheumatoid arthritis
18	..	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
19	+	+	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
20	+	0	Increased (fatty acid)	.....	.....	.....	.....	.....	.....	.....	.....	.....
21	+	..	.....	.....	.....	Decreased albumin; increased gobulin	.....	.....	.....	.....	Deficiency pattern	.....
22	+	..	.....	.....	.....	.....	.....	.....	.....	Hemolytic anemia	.....	.....
23	+	+	Increased	Decreased	Increased	Decreased albumin	Normal	Decreased	Increased tolerance	Antistreptolysin titer, 450	.....	.....
24	+	+	Increased	.....	Increased	Decreased	Decreased	.....	Increased	.....	Normal	.....
25	0	+	?	.....	.....	Decreased albumin	.....	Normal	Increased tolerance	Fecal pigment normal	Deficiency pattern	.....
26	+	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
27	+	0	Normal	Decreased	Normal	Decreased albumin	Decreased	.....	Normal tolerance	Vitamin A tolerance normal; fecal nitrogen normal	Normal	.....
28	0	0	Normal	Normal	Increased	Decreased	Normal	.....	Normal tolerance	Vitamin A tolerance normal; fecal nitrogen normal	Colon normal	.....
29	+	+	Normal	Normal	Increased	Normal	.....	.....	.....	Vitamin A tolerance normal; fecal nitrogen normal	Normal	.....
30	..	..	Increased (neutral)	.....	.....	.....	.....	.....	.....	.....	.....	.....
31	+	+	Normal	.....	Increased	Decreased	Normal	Normal	.....	.....	Deficiency pattern	.....
32	+	..	Increased (neutral)	Decreased (cholesterol)	Increased	Decreased albumin	Decreased	.....	Increased tolerance	.....	Deficiency pattern	.....
33	+	..	.....	.....	.....	.....	.....	.....	Normal tolerance	.....	.....	.....
34	+	+	Normal	Normal	Increased	Decreased albumin	Decreased	Normal	Decreased and increased tolerance	Thymol turbidity, 0	Deficiency pattern	.....

* For key to symbols and authors, see table 2.

of 50 pounds (22.7 Kg.) during the preceding fourteen months. Moderately severe diarrhea had been noted for two months, consisting of four to eight stools daily, usually light colored and nonbulky, without mucus, blood or abdominal cramps. There were recurrent exacerbations during this period, lasting three to four days. A chronic cough productive of a moderate amount of mucopurulent sputum had been present several months.

The past history revealed malaria at 17 years of age, gonorrheal urethritis at 30 without sequelae and the excessive use of alcohol until 1944. There was no history of arthritis. However, the patient complained of considerable generalized muscular aching during the period of hospitalization.

Physical examination showed great emaciation, a sallow color and generalized scaly follicular hyperkeratosis of the trunk and extremities. Temperature and pulse rate were normal. There were complete edentia and poor oral hygiene, but no glossitis was present. The chest was emphysematous and the heart sounds were distant but without murmurs. Blood pressure was 94 systolic and 68 diastolic. The abdomen was flat and tympanitic, with a leathery or doughy sensation to palpation. Results of rectal examination including proctoscopy were not remarkable. There was generalized, mild discrete lymphadenopathy.

Laboratory and roentgenologic findings were as follows: The hemoglobin concentration was 11.7 Gm., with 3,800,000 red blood cells. There was no free gastric hydrochloric acid after administration of histamine. White blood cells numbered 8,100, with a normal differential count. Total cholesterol was 140 mg., cholesterol esters 65 mg., blood urea nitrogen 24 mg., total protein 5.1 mg., with albumin to globulin ration of 1.7: 1, and serum calcium 7.5 mg., per hundred cubic centimeters. The prothrombin time was 100 per cent of normal. In the oral dextrose tolerance test, fasting blood sugar was 95 mg. per hundred cubic centimeters; at one-half hour the level was 110 mg., at one hour 130 mg., at two hours 125 mg. and at three hours 125 mg. The thymol turbidity reading was 0. Total serum lipids were 19 units (turbidimetric method).[8] The test with sulfobromophthalein (bromsulphalein®) sodium U. S. P. showed 32 per cent retention in forty-five minutes after administration of 5 mg. of dye per kilogram of body weight. Quantitative twenty-four hour fecal fat measured 1.1 per cent (wet method), with 0.9 per cent free fatty acid and 0.2 per cent combined fatty acid. However, it should be noted that the patient's food intake was low; it could not be accurately controlled in regard to fat content, and a mild exacerbation of diarrhea was in progress. Serial roentgenograms of the small bowel revealed a "deficiency pattern." Roentgenograms of the upper part of the gastrointestinal tract and examinations with a barium sulfate enema showed a normal appearance.

The patient received intensive supportive, dietary, vitamin and symptomatic therapy to no avail. He had two exacerbations of his diarrhea, becoming acidotic with the last. Although electrolyte and acid-base balances appeared to be restored a few days later, he became stuporous and somnolent; however, his apparent mental clarity when purposely roused was in striking contrast. A fine purpuric rash appeared over the chest and abdomen, and he suddenly and unexpectedly died the next day, Jan. 21, 1949, one month after his admission to the hospital.

Autopsy Observations.—External examination revealed an extremely emaciated body of a 50 year old white man, weighing about 110 pounds (49.9 Kg.) and measuring 71 inches (180 cm.). Severe wasting was manifested by conspicuous bony promi-

8. Kunkel, H. G.; Ahrens, E. H., Jr., and Eisenmenger, W. J.: Application of Turbidimetric Methods for Estimation of Gamma Globulin and Total Lipid to Study of Patients with Liver Disease, Gastroenterology **11**:499-507 (Oct.) 1948.

nences and sunken eyeballs and temples, as well as sunken intercostal spaces. There was slight pitting edema of both ankles. Numerous petechiae were scattered throughout the pale thin skin. These were concentrated particularly over the anterior part of the chest and around an old appendectomy scar in the right lower abdominal quadrant. There were also small submucosal hemorrhages over the bulbar conjunctivas and on the soft palate. A single firm node about 2 cm. in diameter was felt in the left axilla.

The subcutaneous fat was scanty. The pleural and peritoneal cavities contained clear thin fluid. There were 200 cc. in the left side of the chest, 500 cc. in the right side and about 1,500 cc. in the abdominal cavity. The pericardial cavity was completely obliterated by a thick layer of soft, moist, gray, gelatinous connective tissue. There were also many adhesions between the dome of the diaphragm and the liver and spleen. A single adhesive band 4 cm. long was seen in the left pleural cavity at the level of the second rib.

Examination of the viscera revealed verrucous endocarditis involving the aortic, mitral and tricuspid valves. Only the pulmonary valve was spared. The vegetations were firm and well adherent to the cusps at the line of closure. Their surfaces appeared finely lobulated and polished. They were sessile and broad based in the mitral and tricuspid valves. A pedunculated bilobed nodule about 3 mm. in diameter was attached to the posterior aortic cusp. The edges of the valvular cusps were thickened and rolled. A small shallow ulceration was noted on the posterior mitral leaflet.

The aorta showed trivial atheromatous changes with an ulcerated plaque just above the bifurcation.

The lungs were voluminous and heavy (the right weighed 1,250 Gm. and the left 1,100 Gm.). The anterior portions of the upper lobes of both lungs and of the middle lobe of the right lung were well aerated. The remainder of the lungs, however, was heavy, wet and dark red, with gray mottling throughout. Several discrete, firm nodules, measuring between 0.5 and 3 cm., were scattered throughout the pulmonary parenchyma. The largest ones were situated in the posterior segments. On cut surface the nodules appeared dark, red, firm and homogeneous. The trachea and bronchi contained a moderate amount of yellow mucoid secretion. The mediastinal lymph nodes were somewhat enlarged and the cut surfaces showed black discoloration.

The gastrointestinal tract revealed no conspicuous gross lesions in the intestine itself. However, the mesentery was most unusual. The root of the mesentery was greatly thickened, white and firm. Numerous large, discrete, oval-shaped nodes, measuring from 2 to 6 cm. in diameter, could be felt throughout the proximal portion of the jejunal mesentery. In addition, there were numerous small discrete nodules scattered along the intestinal attachment. The fatty deposits were greatly depleted, and the nodes were matted together by grayish pink firm fibrous tissue (fig. 1). The cut surfaces of the nodes were pale yellowish tan, with numerous minute cystic spaces scattered throughout which gave them a spongy appearance (fig. 2). Similar groups of lymph nodes were seen in the retroperitoneal tissue on both sides of the abdominal aorta (fig. 3). The retroperitoneal fat was also depleted. The other abdominal and pelvic viscera were not remarkable, with the exception of the gallbladder, which appeared distended and contained about 30 mulberry-shaped, friable concretions, measuring 0.3 to 1 cm. The serosa of the gallbladder was white and thick. The biliary passageways were patent. No gross lesions were noted in the spleen, adrenal glands, kidneys, ureters, bladder or prostate.

Examination of the cranial cavity revealed nothing unusual.

Fig. 1.—Photograph of mesentery showing the contours of enlarged lymph nodes.

Fig. 2.—Cross section of abdominal lymph nodes showing spongy architecture due to fatty deposits.

Histologic examination confirmed the observation of polyserositis (fig. 4) involving the pleural, peritoneal and pericardial cavities and increasing in degree of involvement in that order. The serous membranes were thickened and composed of a loose reticular connective tissue, consisting of fairly young plump fibroblasts and infiltrated by lymphocytes, plasmacytes and large mononuclear cells with a fairly abundant eosinophilic cytoplasm and round eccentric nuclei. The same pattern was repeated in sections of the pericardium, pleura and hepatic and splenic capsules. Sections of the myocardium revealed a mild interstitial infiltration with lymphocytes and monocytes. The valves of the heart showed thickening and compact broad-based vegetations composed of dense fibrinoid material pierced by some fibroblasts and capillaries at the base (fig. 5).

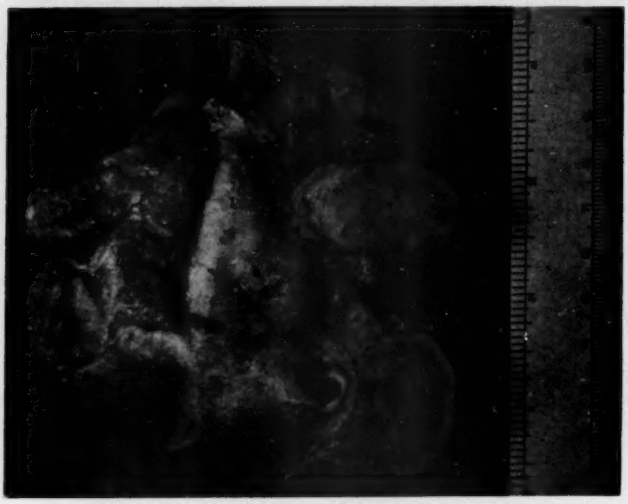

Fig. 3.—Group of enlarged periaortic lymph nodes.

The lungs revealed bronchopneumonia of the aspiration type, with large areas of the parenchyma involved in far advanced necrotic changes and with collections of pus and colonies of micro-oganisms scattered throughout.

The liver showed no parenchymal lesions. The hepatic capsule was involved in the polyserositis described previously.

The spleen, in addition to the capsular changes, showed considerable deposition of hemosiderin which was engulfed by large macrophages scattered in small groups throughout the pulp. There were also eosinophilic hyaline deposits in the follicles.

The pancreas revealed a mild interstitial infiltration with lymphocytes.

The gallbladder had chronic inflammatory changes masked to some extent by autolysis.

The adrenal glands showed depletion of the lipid droplets in the cortical cells, as well as depletion of the adipose tissue around the glands.

No lesions were seen in the thyroid, the genitourinary tract or the central nervous system.

The gastrointestinal tract and mesentery had most interesting changes. Sections of stomach and duodenum were not remarkable. Sections of the small intestine revealed the presence of large lipophages in the mucosal stroma. The mucosal crypts were displaced by the deposits of lipophages and the villi appeared thickened and blunted (fig. 6). The mesenteric and periaortic lymph nodes showed complete obliteration of the usual nodal architecture by large vacuoles

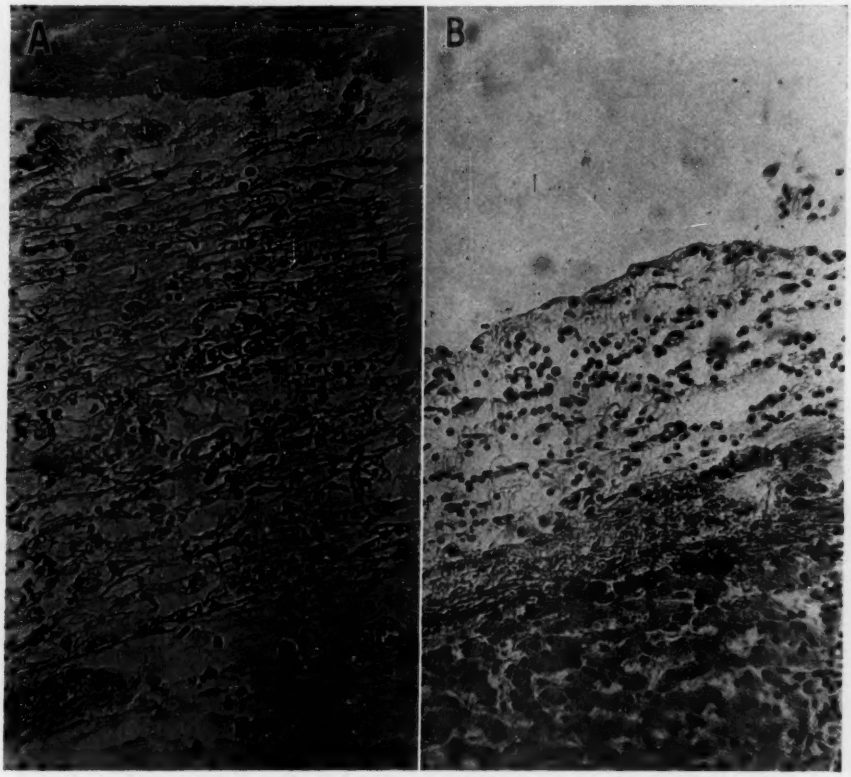

Fig. 4.—Photomicrographs of (*A*) pericardium and (*B*) capsule of liver showing infiltration by lymphocytes, plasmacytes and large mononuclear cells in a loose reticular connective tissue; × about 88.

filled with a fatty substance. The vacuoles varied somewhat in size, but they were scattered uniformly and densely throughout the lymph node parenchyma, imparting a lacy appearance to the lymphoid tissue (fig. 7). Many giant cells of the type resulting from reaction to a foreign body were seen. The giant cells were not so ubiquitous as in material from the case of Apperly and Copley,[1n] supplied to us by

Fig. 5.—Photomicrograph of broad-based vegetation on mitral valve; × about 29.

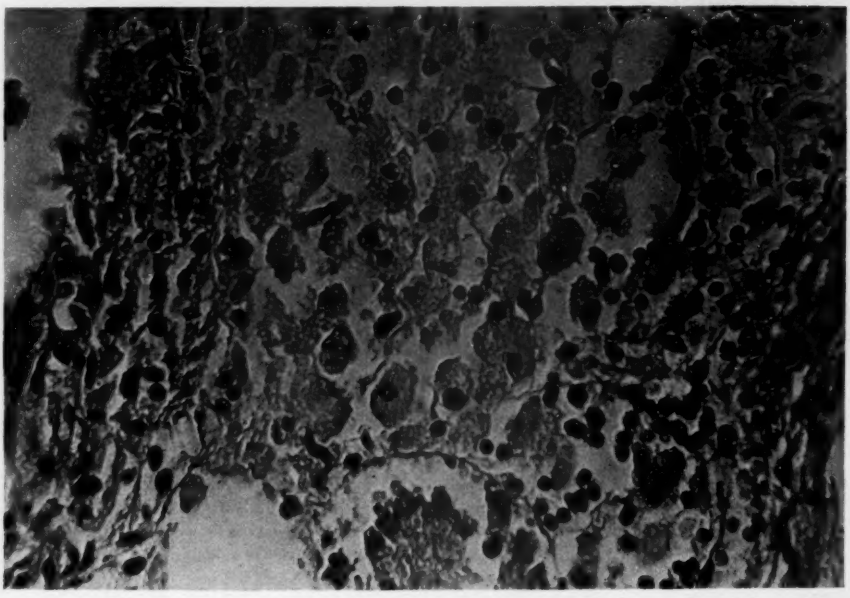

Fig. 6.—Photomicrograph of jejunal mucosa showing infiltration of stroma by large lipophages which displace mucosal crypts; × about 183.

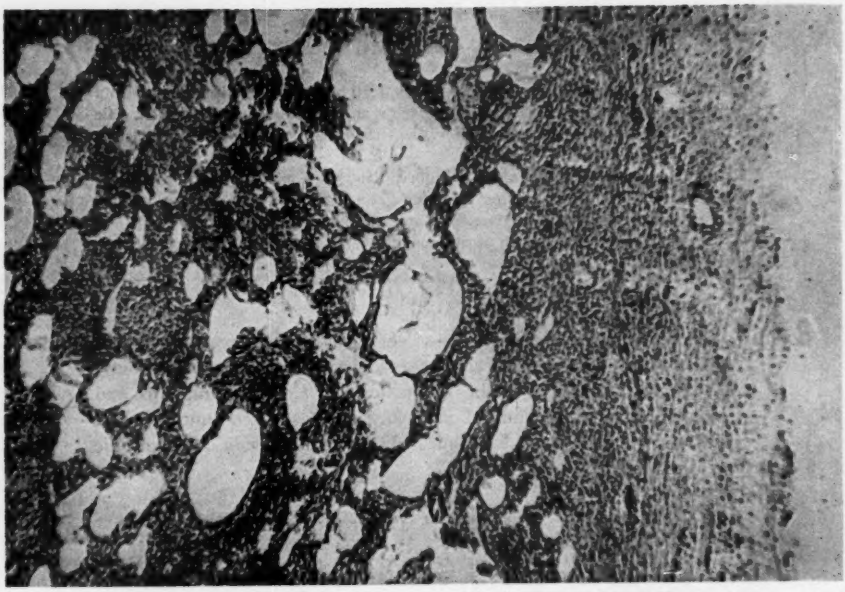

Fig. 7.—Photomicrograph of segment of mesenteric lymph node showing distortion of architecture by fatty deposits and depletion of mesenteric fat proper; × about 29.

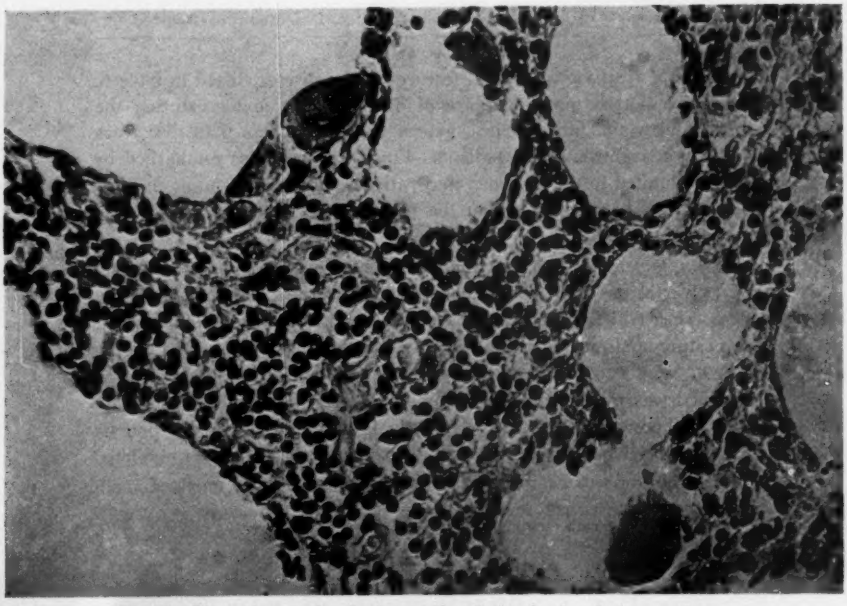

Fig. 8.—Photomicrograph of giant cells of the foreign body reaction type associated with some of the fatty deposits in mesenteric lymph node; × about 183.

the authors. However, they were a constant feature (fig. 8). There were also a few groups of mononuclear lipophages, with an abundant finely granular pale cytoplasm in some of the sections. Results of chemical analysis of the lymph node are shown in table 5.

On final analysis of the autopsy observations, the most important pathologic findings can be classified into three groups: (1) polyserositis, (2) endocarditis and (3) lipogranulomatosis of the intestinal and abdominal lymph nodes

The other observations, such as atheromatosis and chronic cholecystitis, as well as the bronchopneumonic process, are considered incidental.

CLINICAL FEATURES

The frequency and consistency of certain clinical aspects are emphasized because only thereby can one establish a tentative clinical diagnosis, generally thought to be impracticable. Certain symptoms and signs seen sufficiently unusual in themselves, or in conjunction with others, to provide a basis for clinical differentiation from other chronic diarrheal diseases.

TABLE 5.—*Chemical Analysis of Mesenteric Lymph Node*

Constituent	Percentage
Protein (N × 6.25)	7.65
Total fat	31.2
Total fatty acids	24.4
Free fatty acids	< 1.3
Phospholipid (calculated from fat-soluble phosphorus)	< 2.0
Neutral fat (total fatty acids minus free fatty acids and phospholipid)	21.1 +
Dry weight	48.3

General Features.—General features of the disease, listed in table 6, indicate a notable preponderance of 81.8 per cent in men during the third, fourth and fifth decades, with a duration of less than five years in about two thirds of the patients. Final diagnosis was established by autopsy limited to the abdomen in 3 patients and by laparotomy in 5, or a total of 8 patients in whom the pathologic changes of the thoracic viscera are unknown.

Symptomatology.—The symptoms (table 7) are represented chiefly by polyarthritis and intermittent chronic diarrhea and frequently by steatorrhea (oftener than not, unspecified) and abdominal pain described as postprandial and ill defined, with subjective distention. Progressive loss of weight occurred in 31 patients, or 91.1 per cent, and when specified was mild (below 30 pounds [13.6 Kg.]) in only 5, moderate (30 to 50 pounds [13.6 to 22.7 Kg.]) in 4 and severe (50 to 100 pounds [22.7 to 45.4 Kg.]) in 6. Except for 3 patients,[9] the remainder exhibited all degrees of emaciation, although the amount was unstated. No

9. Pearse.[11] Pemberton and others.[2d]

significant correlation could be discovered between the degree of loss of weight and the duration of illness, the duration of diarrhea or the presence of steatorrhea.

The most significant symptom, polyarthritis, was ordinarily transient and migratory and was often mistaken for rheumatic fever. Occasionally, it was described as recurrent in nature, but it left definite residual structural deformity suggesting rheumatoid arthritis in only 3 persons.[10] Case 1 of Pemberton and his associates [2d] was of questionable duration,

TABLE 6.—*General Features*

	Number	Per Cent
Sex (33 cases):		
Men	27	81.8
Women	6	18.1
Age, Yr. (32 cases)		
Below 30	2	6.2
30 to 40	7	21.8
40 to 50	11	34.3
50 to 60	7	21.8
60 to 70	4	12.5
Above 70	1	3.1
Average age (32 cases), 46.2 yr.		
	Number	**Per Cent**
Duration, Yr. (31 cases)		
Under 5	19	61.2
5 to 10	8	25.8
10 to 20	4	12.9
(Questionable duration)	(3)	....
	Number	Average Duration, Yr.
Cases with polyarthritis *	15	6.5
Cases without polyarthritis †	16	2.1
Whole group	31	4.2
	Number	Per Cent
Final Diagnosis		
Complete autopsy	26	76.4
Autopsy limited to abdomen	3	8.8
Laparotomy	5	14.7

* Two cases of questionable duration omitted.[2d,g]
† One case of questionable duration omitted.[2d]

since the patient had polyarthritis forty-four years prior to the reported illness. In their case 3, the patient had monoarticular changes in one shoulder and is not included among those having polyarthritis. It is striking that polyarthritis appeared as the initial symptom in 50 per cent of the patients and was almost invariably antecedent to diarrhea or abdominal pain, if present at all. A time interval between the two symptoms could be established in 8 patients and varied from two to thirteen years. It is also apparent that for those who manifested arthritis the

10. Whipple.[1a] Sailer and McGann.[1k] Clemmesen.[3g]

disease was of longer duration (average, 6.5 years) compared with the average for those with only pain or diarrhea (2.1 years) and for the whole group (4.2 years).

Constipation in 9 patients either preceded or alternated with diarrhea, except in 2 [1j, k] in whom diarrhea never developed during their illness.

TABLE 7.—*Symptomatology (34 Cases)*

	Number	Per Cent
Polyarthritis:		
Duration, yr., from onset to reported illness (death or lap.), less than 5	4	....
5 to 10	8	....
10 to 15	3	....
Questionable or unspecified	2	....
Total (in 34 cases)	17	50.0
Diarrhea:		
Duration, yr., less than 1	9	....
1 to 5	10	....
More than 5	1	....
Questionable or unspecified	10	....
Total (in 34 cases)	30	88.2
Constipation:		
Alone	2	....
With diarrhea	7	....
Total (in 34 cases)	9	26.4
Weight Loss:		
Amount, lb., less than 30	5	....
30 to 50	4	....
50 to 100	6	....
Questionable or unspecified	16	....
(Average amount, 45 lb.)	..	....
Total (in 34 cases)	31	91.1
Abdominal pain and distention	28	82.3
Initial Symptom:		
Abdominal pain and/or diarrhea	17	50
Polyarthritis	17	50
Other Symptoms:		
Chronic productive cough	7	20.5
Hematuria	2	5.8
Urethritis and blennorrhagia	1	2.9

The initial symptom noted clinically was pain or diarrhea in 50 per cent and polyarthritis in 50 per cent. Diarrhea invariably ensued some months or years after the onset of arthritis except in 1 patient,[1k] in whom only abdominal pain later developed.

Other symptoms less frequently encountered included chronic cough productive of mucopurulent sputum in 7 patients.[11] Gross hematuria occurred in 2 [12] several years prior to death, in one at the onset and in the other during the middle period of the disease.

11. Footnotes 1 *a*, *k* and *o* and 3 *a* and *e*.

12. Sailer and McGann.[1k] Clemmesen.[3g]

Review of the past histories revealed 1 patient with transient jaundice [1e] two years prior to the onset of illness and 1 with hemolytic anemia requiring splenectomy [1o] shortly before onset of the terminal illness. This same patient had a peculiar lymphoblastosis, which at one time was thought to represent lymphatic leukemia. Two patients [1g] had clinical hepatic cirrhosis with splenomegaly antecedent to and concurrent with lipophagic granulomatosis.

Eleven patients were subjected to laparotomy either prior to or during the terminal illness because of the observation of an abdominal mass or other more elusive indication. A biopsy diagnosis of lipophagic granulomatosis was established in 7 [14] of these at laparotomy. The disorders in 3 others [15] were diagnosed at operation as Hodgkin's disease,

TABLE 8.—*Physical Signs (34 Cases)*

	Number	Per Cent
Emaciation	26	76.4
Hypotension	22	64.7
Purpura	17	50.0
Lymphadenopathy	14	41.1
Pigmentation	16	47.0
Edema	13	38.2
Fever	6	17.6
Abdomen, Mass	9	26.4
"Doughy"	4	11.7
Glossitis	3	8.8
Tetany	3	8.8
Arthritis	3	8.8
"Sudden" death	10	29.4
Central nervous system disorder	3	....
Cardiorespiratory cause	4	....
Unspecified type	3	....

Boeck's sarcoidosis and healed tuberculous adenitis or ileitis, respectively. Subsequent to diagnosis at laparotomy, 5 of these 7 patients were given roentgen therapy,[16] without benefit in 2.[17] Two patients [18] were operated on for chronic gallbladder disease prior to clinical onset of lipophagic granulomatosis. Another, mentioned previously,[1o] had a splenectomy for chronic hemolytic anemia.

Physical Signs.—Physical signs (table 8), usually indefinite and insidious, nearly always included some degree of emaciation unless the patient was seen at an early stage. Two of the patients of Pemberton and collaborators [2d] showed no appreciable loss of weight, a finding

13. Reinhart and Wilson.[1j] Rosen and Rosen.[2a]
14. Footnotes 1 *c*, *h* and *l* and 2 *b* and *d*.
15. Apperly and Copley.[1n] Amsterdam and Grayzel.[1p] Newman and Pope.[2e]
16. Footnotes 1 *c* and *h* and 2 *b* and *d*.
17. Comfort, M. W.: Personal communication to the authors.
18. Vaux.[1m] Pemberton and others.[2d]

which was attributed to the short duration of the disease at that time. Hypotension (systolic pressure below 100) was present in 22 patients (64.7 per cent). Another consistent sign, generalized "muddy" or sallow gray pigmentation of the skin, occurred in 16 (47 per cent).

An indefinite plastic or doughy abdominal mass was perhaps the most tangible and significant observation, especially when accompanied with other signs just mentioned. This type of mass was present in 9 patients, while 4 were described as having a doughy or leathery sensation to palpation of the abdomen. Among the 9 patients with definite masses, 2 had masses in the epigastrium and 2 in the midabdomen, 1 each in the left upper abdominal quadrant, left lower quadrant and right lower quadrant, with the location in the remaining 2 patients unspecified.

Generalized discrete lymphadenopathy occurred in 41 per cent and dependent edema in 38 per cent of the patients. Purpura, although

TABLE 9.—*Laboratory Findings (34 Cases)*

	Number with Significant Result	Number of Cases with Test Specified
Secondary anemia	27	29
Gastric achlorhydria	15	20
Increased fecal fat	11	17
Low serum lipids	3	6
Low serum proteins	3	10
Albumin to globulin reversal	2	10
Hypocalcemia	5	9
Low dextrose tolerance curve	5	9
Normal vitamin A tolerance	3*	3
Normal fecal nitrogen	3*	3
Roentgenography: Small bowel "deficiency" pattern	7	12

* Thought to have been early cases.[2d]

frequent (50 per cent), was ordinarily manifested during the terminal period of illness. Chronic polyarthritis with structural joint changes was noted in 3.[10]

The usual absence of fever (fever was reported in only 17.6 per cent)[19] and of glossitis (reported in 8.8 per cent) is noteworthy. Tetany was noted in only 3 patients,[20] 1 of whom had hypocalcemia.

"Sudden," or in essence clinically unexpected, death marked the course of 10 patients (table 8). Of these, the deaths of 4 appeared clinically to be from respiratory causes,[21] while 3 other patients, including ours, had symptoms referable to the central nervous system. The remaining 3 deaths fell in no typical pattern.

Results of Laboratory Study.—Clinical laboratory data, shown in table 9, were at best nonspecific, and when abnormal they were consistent

19. Footnotes 1 *e* and *p* and 2 *f* and *g*.
20. Blumgart.[1b] Newman and Pope.[2e]
21. Footnotes 1 *a*, *j* and *n* and 2 *a*.

with those found in many diarrheal diseases and associated nutritional deficiency. Secondary anemia was almost the rule (93 per cent), either hypochromic or normochromic, but usually of the iron deficiency type. Deviation from this pattern occurred in 1 patient with hemolytic anemia,[10] but macrocytic anemia was observed in none. Gastric anacidity to either a test meal or histamine was noted in 15 patients, and free hydrochloric acid was present in 5, these signs not being specified in the remainder. Gastric achlorhydria was present in 6 of the 11 patients with steatorrhea.

The amount of fecal fat was ascertained in 17 patients and steatorrhea was detected in 11 of these. Of those with steatorrhea, the amount was unspecified in 5. In 6 others results of fecal fat determinations varied from 26 to 80 per cent of dry weight per twenty-four hour specimen. Fractionation of fecal fat in 5 of these revealed 3 with preponderantly neutral fat and 2 with mostly fatty acid in the stools. In addition to those 11 in whom steatorrhea was specified, there were others who, from the gross description of the stools, possibly had steatorrhea although it was not so mentioned. Incompleteness of the data prevented any reliable comparison with the blood chemical values in these 11 patients with steatorrhea.

Fasting serum lipids were low in 3 of 6 patients in whom they were determined. One of these also had increased fecal fat; all 3 had lowered serum calcium and low serum protein levels. In none was there any significant alteration in the proportions of cholesterol, phospholipids or fatty acids.

Blood urea nitrogen was moderately elevated in 7 of 8 determinations, and nonprotein nitrogen was within normal range in 3 others. Total serum protein was lowered in 8 of 10, with a reversal of the albumin to globulin ratio in 2,[22] and a decrease of the ratio in 5 due to reduction in the albumin fraction.

Of 9 patients with serum calcium determinations, total calcium was significantly reduced in 5, only 1 of whom manifested tetany[1b] and 2 steatorrhea. Prothrombin time was low in 1 of the 4 on whom this determination was made.

Among 9 patients on whom dextrose tolerance tests were performed, normal results were obtained in 3, low values in 5 and a borderline low curve in 1. There were insufficient data for comparison with fecal fat content, and the few determinations on the same patient showed no apparent correlation. Random fasting blood sugar levels were greatly decreased in 2 patients.[23]

22. Amsterdam and Grayzel.[1p] Oliver-Pascual and others.[2b]

23. Blumgart.[1b] Pemberton and others.[2d]

Miscellaneous laboratory data may be found in table 4. Of special interest are the occasional occurrence of eosinophilia [24] and the one instance each of elevated antistreptolysin [3g] and hemolytic anemia in

TABLE 10.—*Pathologic Data in Thirty-Four Cases* *

Case No.	Lipogranulomatous Mesenteric Nodes	Jejunoileal (or Mesenteric) Lipodeposition	Fibrous Peritonitis	Fibrous Pleuritis	Fibrous Pericarditis	Verrucous Endocarditis	Chylous Ascites	Extra-alimentary Lipodeposition	Infarcted Viscera	Other Lesions
1	+	+	+	+	+	+	..	spl	..	.....
2	?	?	..	NE;A	NE;A	NE;A	..	..	..	atr, spl
3	+	+	..	..	+	..	+	..	k	atr, spl
4	+	+	..	..	..	..	..	..	..	atr, spl
5	+	..	+	+	+	..	..	..	..	.....
6	+	..	..	+	+	..	..	..	..	.....
7	+	..	..	NE;A	NE;A	NE;A	..	..	..	.....
8	+	+	..	+	+	+	..	..	..	.....
9	+	+	..	+	..	..	..	..	..	.....
10	+	+	..	..	+	+	..	med	..	.....
11	+	+	..	..	..	..	..	..	..	.....
12	+	..	+	..	+	..	..	spl	..	perispl
13	+	+	+	+	..	..	..	..	..	.....
14	+	+	..	..	..	+	..	..	spl	.....
15	+	+	+	NE;A	NE;A	NE;A	..	..	spl	.....
16	+	+	per	+	+	+	..	..	..	perispl
17	+	+	..	+	+	..	+	..	..	atr, spl
18	..	..	..	NE;L	NE;L	NE;L	..	per	..	.....
19	+	+	+	0	0	0	..	..	..	m.g.
20	+	+	..	+	+	0	..	..	..	.....
21	+	+	+	0	0	..	..	br, adr	spl, k, lu	.....
22	+	+	+	..	..	0	..	..	..	.....
23	+	+	0	0	0	+	.	lu	k	m.g.
24	+	+	+	0	0	NE;L	0	..	..	.....
25	+	+	+	NE;L	NE;L	0	+	..	..	.....
26	+	+	+	+	0	NE;L	..	..	..	.....
27	NE;L	(+)	..	NE;L	NE;L	NE;L	..	..	..	.....
28	NE;L	(+)	..	NE;L	NE;L	NE;L	..	..	..	.....
29	NE;L	(+)	..	NE;L	NE;L	0	..	..	..	.....
30	+	+	+	+	+	0	..	..	..	.....
31	+	+	+	+	0	0	..	..	..	atr, spl
32	+	+	+	+	+	0	..	spl, lu, li	..	.....
33	+	+	..	..	+	..	..	..	..	m.g.
34	+	+	+	+	+	+	0	..	..	atr, spl
Total no. specified	29	25 (3)	17	18	21	14	5	..	..	.....
Total no. with lesion	29	25 (3)	15	14	15	7	3	..	..	.....
Per Cent	100	100	88	78	71	50	60	..	..	.....

* Explanation of symbols: +, present; 0, absent; NE, not examined; A, autopsy; L, laparotomy; spl, spleen; med, mediastinum; per, peritoneum; adr, adrenal gland; lu, lung; li, liver; perispl, perisplenitis; br, bronchial nodes; k, kidney; atr, atrophy; m.g., miliary granuloma.

combination with lymphogenous blood dyscrasia.[10] A thymol turbidity reading of 0 was also recorded for our patient, probably the result of low serum lipid content.

24. Whipple.[1a] Clemmesen.[3g]

Roentgenologic studies of the small bowel in 11 patients revealed a so-called deficiency pattern in 7. Two presented roentgen findings in the joints, confirming a clinical impression of rheumatoid arthritis.[1a, k] Another had roentgenologic signs of rheumatoid arthritis in one shoulder.[2d]

Pathologic Features.—These are tabulated in table 10. In addition to the lipogranulomas, especially noteworthy is the frequency of polyserositis, verrucous endocarditis, infarcted viscera and miliary granulomas.

COMMENT

Diagnosis.—The concept of lipophagic granulomatosis as a pathologic entity seems fairly well established as a result of several independent studies.[25] Although previous publications have occasionally postulated a fairly definite clinical pattern,[26] until now insufficient data have been available to formulate a numerically reliable basis for its existence as a clinical entity. It is our impression that only certain of the features in these 34 patients occur with such regularity in a sufficiently large group to provide the basic foundation for such a diagnosis. With moderate or far advanced disease, such a diagnosis appears feasible with reasonable certainty from only the clinical history and physical signs. To our knowledge, a clinical diagnosis was considered for only 1 other of the 34 patients, [2f] one of us (W. H. H.) having suggested the proper diagnosis for our patient.

Several characteristics in tables 6, 7, 8 and 9 stand out in diagnostic value by either their incidence or their nature. These features might be listed roughly in order of importance thus: sex, polyarthritis, steatorrhea, hypoadrenocortical symptom complex, abdominal findings, hypothermia or normothermia, absence of glossitis and secondary anemia.

From the incidence of the various characteristics, it is apparent that this disease entity occurs predominantly in men between the ages of 40 and 60. Its beginning is marked by either transient polyarthritis or postprandial pain and diarrhea, which results a few years later (if the former) or several months later (if the latter) in progressive cachexia and death.

Steatorrhea has a frequency approaching 75 per cent, thus assuming an integral place in the symptom complex. Differential diagnosis, therefore, demands that it be distinguished from sprue, spruelike disorders and pancreatic insufficiency, as well as from the diseases manifesting nonfatty diarrhea, abdominal pain and progressive asthenia. For simplicity, similar disturbances may be divided into three groups: the

25. Footnote 1*e*, *j* and *k*. Rosen and Rosen.[2a] Clemmesen.[2g]
26. Footnotes 1*k*, *n* and *p* and 3 *g*.

steatorrhea group (sprue, idiopathic steatorrhea, symptomatic sprue and pancreatic disease), the enterocolitis group (infectious enterocolitis, the nonspecific ulcerative variety and stenosing jejunoileitis) and the endocrine group (panhypopituitarism, adrenocortical insufficiency).

The first group includes tropical and nontropical sprue, essentially the same disease except for geography. Contrasted to lipophagic granulomatosis, in sprue there are the climatic factor and absence of hypotension, pigmentation or abdominal mass. Arthritis is a late manifestation. Glossitis and macrocytic anemia are usual, and the therapeutic response to specific erythrocyte maturation factor is even more striking. Natural remissions are common, and the bowel disturbance may often be traced to childhood.

Symptomatic sprue is based etiologically on extensive obstruction of lacteals or mesenteric glands,[27] and occasionally on blockage at the cisterna chyli or lower thoracic duct. The former includes widespread mesenteric lymphoma, tuberculous mesenteric lymphadenitis, lymphangioma, chylous cysts and nonspecific sclerosing lymphangitis or lymphadenitis. Obstruction of the thoracic duct or cisterna is secondary to parasitic obstruction (e. g., filariasis), trauma or neighboring tumor. These types of symptomatic sprue are the most difficult to differentiate from lipophagic granulomatosis. All are rare, but they do not ordinarily exhibit arthritis, sex predilection, hypotension or pigmentation. Fever is commonly present and chylous ascites frequent. The primary causative factor is often obvious (e. g., Hodgkin's disease, cervical tuberculous adenitis, tumor). In some cases, laparotomy is necessary for differential diagnosis.

Pancreatic insufficiency, as a cause for steatorrhea and loss of weight, produces symptoms depending on the causative lesion. There is absence of arthritis and pigmentation and, frequently, of roentgenologic signs indicative of tumor. Pancreatic pain is quite different in character and location. Duodenal amylase and lipase following secretin stimulation are low in some instances, while in the serum these enzymes are often high. Either gross or quantitative chemical estimation of the fecal fat fractions is not a reliable indicator of pancreatogenic steatorrhea, as shown by Andersen.[28] Fractional fecal fat analyses in 5 patients of this group reviewed seem to confirm Andersen's studies. In pancreatic carcinoma diabetic dextrose tolerance curves have been noted by Berk

27. Fairley, N. H., and Mackie, F. P.: Clinical and Biochemical Syndrome in Lymphadenoma and Allied Diseases Involving Mesenteric Lymph Glands, Brit. M. J. **1**:375-380 (Feb. 20) 1937.

28. Andersen, D. H.: Cystic Fibrosis of Pancreas and Its Relation to Celiac Disease: Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938.

in 78 per cent,[29] in direct contrast to the high dextrose tolerance of lipophagic granulomatosis. Pancreatic steatorrhea is frequently associated with creatorrhea, which may be detected microscopically in the stool.

In the enterocolitis group, including regional ileitis, steatorrhea is unusual and the stools are often bloody. Polyarthritis, if present, always follows the diarrhea. Perforation or obstruction often occurs and the roentgenologic signs of stenosing ileitis are characteristic. Cultures of the stool are helpful in specific varieties.

Lipophagic granulomatosis reveals many characteristics resembling pituitary and adrenocortical hypofunction (hypotension, pigmentation, asthenia, male predilection, abdominal pain), but differentiation is not difficult when attention is focused on the type of pigmentation, the rarity

TABLE 11.—*Theories of Pathogenesis*

Chemical	Whipple [1a]	Fat containing toxic substance or chemically abnormal fat
	Korsch [1g]	Functional alteration of pancreatic lipase → abnormally split interstitial fat → foreign body inflammation
	Saller and McGann [1k]	Local necrosis of fat tissue → lipolytic ferments
	Apperly and Copley [1n]	Faulty resynthesis → retention of free fatty acids → inflammatory reaction → fibrosis
Hyperfunctional	Reinhart and Wilson [1j] Escudero and others [2f]	Increased intestinal excretion and reabsorption of fat
Mechanical	Hill [1f]	Lymphangitis (? bacterial) → fibrotic obstruction → chylangiectasis
	Jarcho [1e]	Obstructive chylangiectasis, ? congenital
	Rosen and Rosen [2a]	Partial obstruction (?) of thoracic duct
	Chapnick [2f]	Mesenteric lymphatic obstruction, acquired, ? cause
	Clemmesen [2g]	Pararheumatic type inflammation → mesenteral fibrosis → obstruction

of steatorrhea (or diarrhea), the presence of abdominal mass or arthritis and the serum concentration of sodium and potassium.

Pathogenesis.—Previous Theories: In recognition of the preceding data and the morphologic characteristics noted in table 10, it normally follows that any discussion of pathogenesis would be an inferential interpretation of the clinicopathologic features.

Previously postulated theories (table 11) are not supported by experimental or clinical studies and there has been no investigative work concerning this disorder. We are thus reduced to a comparative study of these clinicopathologic characteristics with those of disorders known to bear a common resemblance in their basic features.

In our opinion, the studies cited later tend to refute previous hypotheses of pathogenesis. The view that the mesenteric lesions of this

29. Cited in Bockus, H. L., and others: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1946, vol. 3, p. 823.

disease are caused by obstruction of the thoracic duct finds no confirmation in clinical or experimental works on man and animal.[30] The concept of faulty resynthesis and fatty acid depositions tends to be discounted by the fat absorption studies of Frazer and others,[31] plus the fact that the lipogranulomas in this disease contain almost entirely neutral fat and not free fatty acids.[1a, n] The theory of increased excretion and reabsorption cannot be disproved, but there is evidence that intestinal excretion of fat is concerned largely with unsaponifiable lipids,[31g] which have not been present to significant degree in the mesenteric lesions [1a, n] (table 5).

Clemmesen's concept of pararheumatic disease, with the chief focus of inflammation the mesenteric lymphatic system, might suggest fibrotic obstruction and perhaps also explain the cardiovascular lesions. But it has not been demonstrated that a nonspecific mesenteric lymphadenitis or lymphangitis can produce fat deposition of this sort.[32] The discussion to follow appears to be more in accord with the clinicopathologic picture, the recent fat absorption studies just mentioned [31] and other reports referred to later.

Resemblances to Other Diseases: Lipophagic granulomatosis has various aspects which resemble other disorders, chiefly, (1) collagen diseases (notably, rheumatic fever, drug sensitivity, rheumatoid arthritis

30. Blalock, A.; Robinson, C. S.; Cunningham, R. S., and Gray, M. E.: Experimental Studies on Lymphatic Blockage, Arch. Surg. **34**:1049-1071 (June) 1937. Freeman, L. W.: Lymphatic Pathways from Intestine in Dog, Anat. Rec. **62**:543-550 (April 25) 1942. Co Tui; Barcham, I., and Shafiroff, B. G. P.: Ligation of Thoracic Duct and Posthemorrhage Plasma Protein Level, Surg., Gynec. & Obst. **79**:37-40 (July) 1944. Drinker, C. K.: Extra Vascular Protein and Lymphatic System, Ann. New York Acad. Sc. **46**:807-821 (Sept. 16) 1946.

31. (*a*) Frazer, A. C.: Differentiation in Absorption of Olive Oil and Oleic Acid in Rat, J. Physiol. **102**:306-312 (Dec. 31) 1943. (*b*) Frazer, A. C.; Schulman, J. H., and Stewart, H. C.: Emulsification of Fat in Intestine of Rat and Its Relationship to Absorption, ibid. **103**:306-316 (Dec. 15) 1944. (*c*) Frazer A. C.: Lipolysis and Fat Absorption, ibid. **102**:329-333 (Dec. 31) 1943. (*d*) Frazer, A. C., and Sammons, H. G.: Formation of Mono- and Di-Glycerides During Hydrolysis of Triglyceride by Pancreatic Lipase, Biochem. J. **39**:122-128, 1945. (*e*) Frazer, A. C.: Absorption of Triglyceride Fat from Intestine, Physiol. Rev. **26**:103-119 (Jan.) 1946. (*f*) Elkes, J. J., and Frazer, A. C.: The Relationship of Phospholipin to the Absorption of Unhydrolysed Fat from the Intestine, J. Physiol. **102**:24P (Nov. 27) 1943. (*g*) Elkes, J. J.; Frazer, A. C., and Stewart, H. C.: Composition of Particles Seen in Normal Human Blood Under Dark-Ground Illumination, ibid. **95**:68-82 (Feb. 14) 1939. (*h*) Cooke, W. T., and others: Anomalies of Intestinal Absorption of Fat: Determination and Significance of Faecal Fat, Quart. J. Med. **15**:141-155 (April) 1946.

32. Wilensky, A. O.: General Abdominal Lymphadenopathy with Special Reference to Nonspecific Mesenteric Adenitis, Arch. Surg. **42**:71-125 (Jan.) 1941.

and disseminated lupus erythematosus), (2) addisonian adrenocortical insufficiency, (3) sprue and idiopathic steatorrhea and (4) the varieties of symptomatic sprue secondary to obstruction of the lacteals.

In consideration of the third aspect, it becomes obvious that the lesions observed in these 34 patients are entirely incompatible with the "lack" of morphologic stigmas seen in either type of sprue and share no etiologic relationship.

Relation to Symptomatic Sprue: The clinical signs and the mesenteric lymphatic lesions suggest that lipophagic granulomatosis, in the final analysis, belongs in the class with symptomatic sprue. The known pathogeneses and similar symptoms of other diseases in that group also tend to support the concept of lacteal obstruction.[27] For that reason, the greatest difficulty in differential diagnosis is among disorders of that class, in spite of their diverse origins. With lacteal obstruction, one expects primarily evidences of deficiency in the fat-soluble vitamins and minerals, such as hypocalcemia, hemorrhagic tendencies, follicular dermatitis, ocular inflammation and osteoporosis. Hypocalcemia may be largely due to faulty absorption of vitamin D rather than to removal of calcium to form insoluble soaps. By contrast, the malabsorption of sprue is total with respect to dietary components. Here deficiencies not only of fat but of carbohydrate, protein and water-soluble vitamins occur during relapse and improve on remission. In lipophagic granulomatosis, at least in the earlier stages, there is no reason to suspect interference with intrinsic factor, vitamins of the B complex or protein absorption through the mesenteric tributaries of the portal system, thus perhaps explaining the usual absence of the stomatitis, glossitis, polyneuritis and macrocytic anemia so often seen in sprue and pellagra. These constitute a valuable differential factor, separating lipophagic granulomatosis from the deficiency diseases with a wide range of absorptive defect.

Johnson and his co-workers postulated that certain absorbed fatty acids have hemolytic properties which may play a part in production of chronic anemia.[33] Of the 25 patients with lipophagic granulomatosis with anemia, all except 1 showed normochromic or hypochromic normocytic types, the excepted patient having acquired chronic hemolytic anemia. That possibility was considered by Fitzgerald and Kinney [10] for the last mentioned patient, but for the other 24 patients the recorded laboratory data do not suggest that chronic hemolysis was a factor in the anemia. However, the usual laboratory criteria for increased hemolysis were not determined in the majority. Josephs and his associates demonstrated increased fecal pigment in infants on a high fat

33. Johnson, V.; Freeman, L. W., and Longini, J.: Erythrocyte Damage by Lipemic Serum in Normal Man and in Pernicious Anemia, J. A. M. A. **124**:1250-1254 (April 29) 1944.

intake [34] and the question is raised whether fat absorption normally plays a part in red cell destruction. Since Frazer's experiments suggested that fatty acids normally are absorbed into the portal system, he and Cooke postulated that hemolysis in the portal blood might occur, therefore giving no evidence of systemic hyperbilirubinemia but producing an increase in fecal pigment.[35]

This mechanism may offer an explanation of the anemia in lipophagic granulomatosis. In obstruction of the lacteals, partial absorption of fat as fatty acids might be accomplished through the portal pathway as Frazer suggested, and this may at the same time explain the absorption of 10 to 64 per cent of the normal amount in 11 of these patients with proved steatorrhea. Another alternative might be on a malabsorptive basis, but in the absence of hemolysis the hemosiderin deposits would suggest adequate iron stores were available but not utilized. Achlorhydria does not seem significant, since there was no consistent relation of gastric anacidity to anemia in the group.

Gillman's concept of the anemia of South African pellagra [36] postulated the absorption of "macromolecular" colloidal iron particles through a damaged intestinal mucosa, with subsequent reexcretion by the liver. This idea is supported by the frequent observation of hemosiderosis in this group of patients and is offered as another explanation of the anemia in lipophagic granulomatosis.

Relation to Rheumatic and Endocrine Disorders: Lipophagic granulomatosis shows numerous resemblances to the "collagen diseases" and adrenocortical hypofunction, as evidenced by the foregoing data. Therefore, it seems logical to postulate a pathogenesis with these basic similarities in mind.

The initial symptomatology and later clinical manifestations, occurring during the middle years of life but pursuing a relatively short course, all suggest that this disorder is acquired rather than caused by an inherent disturbance of fat absorption or metabolism.

The perivasculitis, panserositis, endocarditis and chronic interstitial inflammation probably represent a generalized collagen response to trauma in the broadest sense, the nature of which is unknown but which is productive of profound biochemical disturbances. These lesions and the onset of polyarthritis months or years prior to the gastrointestinal

34. Josephs, H. W.; Holt, L. E., Jr.; Tidwell, H. C., and Kajdi, C.: Influence of Dietary Fat upon Excretion of Urobilin, Bull. Johns Hopkins Hosp. **71**:84-95 (Aug.) 1942.

35. Cooke, W. T., and others: Anomalies of Intestinal Absorption of Fat: Haematology of Idiopathic Steatorrhoea, Quart. J. Med. **17**:9-24 (Jan.) 1948.

36. Gillman, T.; Mandelstam, J., and Gilbert, C.: Cytosiderosis and Genesis of Arteriosclerosis and Other Fibrous-Tissue Reactions, Nature, London **159**:875-876 (June 28) 1947.

symptoms suggest that the intra-abdominal lipogranulomas are also morphologic indications of the same systemic disorder, in some way related to the "collagen diseases" by its clinical and pathologic manifestations.

In these instances somatic response to injurious agents may include not only a proliferative cellular reaction but also the formation of immune substances, as in Clemmesen's patient, who demonstrated one type of specific antibody. The proliferative component of such a response has been shown to occur with a number of biologically foreign agents by Clark and Kaplan,[37] Rich [38] and others.[39] Serosal and vascular lesions of the same order may be seen in patients with lipophagic granulomatosis. It may be significant that the course of this disease is more protracted in those showing polyarthritis initially. This suggests the production of partial immunity through the formation of protective antibodies.

The clinical resemblances to addisonian adrenocortical insufficiency are noteworthy, but a parallel biochemical disturbance in electrolyte balance has not been demonstrated. Nevertheless, the cortical steroids are known to have an essential but undefined role in fat absorption [40] and mobilization.[41] The work of Hench and his group [42] has shown apparent production of clinical remission in patients with active rheumatoid arthritis and rheumatic fever, with the use of 17-hydroxy-11-

37. Clark, E., and Kaplan, B. I.: Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458-475 (Oct.) 1937.

38. Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa as Indicated by 7 Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123-140 (Sept.) 1942; Additional Evidence of Role of Hypersensitivity in Etiology of Periarteritis Nodosa: Another Case Associated with Sulfonamide Reaction, ibid. **71**:375-379 (Dec.) 1942.

39. Merkel, W. C., and Crawford, R. C.: Pathologic Lesions Produced by Sulfathiazole: Report of 4 Fatal Cases, J. A. M. A. **119**:770-776 (July 4) 1942. Black-Schaffer, B.: Pathology of Anaphylaxis Due to Sulfonamide Drugs, Arch. Path. **39**:301-314 (May) 1945.

40. Bavetta, L.; Hallman, L.; Denel, H. J., Jr., and Greeley, P. O.: Effect of Adrenalectomy on Fat Absorption, Am. J. Physiol. **134**:619-622 (Oct.) 1941. Verzór, F., and McDougall, E. J.: Absorption from the Intestine, London, Longmans-Green & Co., 1936.

41. Hartman, F. A.; Brownell, K. A., and Thatcher, J. S.: A New Hormone of the Adrenal Cortex, abstracted, J. Clin. Endocrinol. **7**:461-462 (June) 1947.

42. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Effect of Hormone of Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **24**:181-197 (April 13) 1949. Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, ibid. **24**:277-298 (May 25) 1949.

dehydrocorticosterone (compound E) and pituitary adrenocorticotropic hormone. The concomitant therapeutic reversal of early mesenchymal lesions, similar to the collagen changes of lipophagic granulomatosis, has also been suggested by their investigations. Further studies by Bergner and her associates,[43] using 11-dehydrocorticosterone (compound A), have demonstrated a decided decrease in excretion of fecal fat in adrenalectomized rats maintained with desoxycorticosterone acetate and also in patients with Addison's disease with and without steatorrhea.

It has been demonstrated by Elkes [31f] and others [44] that the hydrophilic nature of certain phospholipids is essential in stabilizing the fat emulsion of the plasma and lacteal fluid. That phospholipids function as an emulsion stabilizer was demonstrated by MacFarlane and Knight (1941), who showed that Clostridium perfringens alpha toxin lecithinase could cause fat flocculation and serum turbidity.[45] In this manner the chylomicron size and the degree of dispersion seem dependent on the phospholipid content of serum or plasma.[44b] Disturbances of the lymphatic or plasma phospholipid may result in fat flocculation and deposition, possibly by alterations in the hydrophilic side chain,[44b] which thus becomes less capable of maintaining an interfacial film conducive to finely dispersed chylomicrons. Although in the plasma hydrolysis of phospholipids by lecithinase would ordinarily produce violent hemolysis,[46] it seems to be possible in the lacteals without the occurrence of such a reaction.

The clinicopathologic pattern, when considered in the light of these investigations,[47] suggests an adrenal relationship among the syndromes of Addison's disease, the rheumatic diseases and lipophagic granulomatosis. In the absence of any demonstrable adrenocortical defect at necropsy, perhaps this is chiefly an "exhaustion" cortical deficiency, as

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43. Bergner, G. E.; Lewis, R. A.; Stout, F. W.; Thorn, G. W., and Emerson, K., Jr.: The Effect of 11-Dehydrocorticosterone on Fecal Fat Excretion, abstracted, J. Clin. Endocrinol. **8**:606 (July) 1948.

44. (*a*) Frazer, A. C., and others: Effect of Cl. Welchii Type A Toxins on Body Tissues and Fluids, Lancet **1**:457-460 (April 14) 1945. (*b*) Ahrens, E. H., Jr., and Kunkel, H. G.: The Stabilization of Serum Lipid Emulsions by Serum Phospholipids, J. Exper. Med. **90**:409-423 (Nov.) 1949. (*c*) Bollman, J. L., and Flock, E. V.: Lipids in the Lymph of Rats, abstracted, Federation Proc. **8**:350 (March) 1949. (*d*) Fish, P. A., and Gage, S. H.: Fat Digestion, Absorption, and Assimilation in Man and Animals as Determined by Darkfield Microscope, and Fat-Soluble Dyes, Am. J. Anat. **34**:1-85 (Sept.) 1924.

45. MacFarlane, M. G., and Knight, B. C. J. G.: Biochemistry of Bacterial Toxins: Lecithinase Activity of Cl. Welchii Toxins, Biochem. J. **35**:884-902 (Sept.) 1941.

46. Ahrens, E. H.: Personal communication to the authors.

47. Hench and others.[42] Bergner and others.[43]

described in the adaptation syndrome by Selye.[48] In this instance there is no apparent deficiency of the steroid fraction controlling electrolyte and water balance as in Addison's disease, but possibly other corticosteroids are involved, such as compounds A and E. Since the organism is known to be hypersusceptible to stress (nonspecific shock) during adrenocortical insufficiency,[48] the frequency of "sudden death" in lipophagic granulomatosis would not be unexpected, if such a pathogenesis is held conceivable. In the terminology of Selye, the postrheumatic remission of lipophagic granulomatosis might be called the phase of resistance and the onset of diarrhea might mark the beginning of the phase of exhaustion.

However, there remains the possibility of a primary insufficiency of pituitary adrenocorticotropic hormone as the basic defect and there are 2 patients in whom such a relationship is suggested. Escudero's [2f] patient had several colloid cysts in the anterior part of the pituitary body and atrophy of the alpha cells in the islets of Langerhans. Oliver-Pascual's patient [2b] also had symptoms suggesting a polyendocrine dysfunction. This patient had an exacerbation of diarrhea during each pregnancy. Termination of the first pregnancy was associated with a prompt and dramatic remission of symptoms for a three year period. It seems that pregnancy might initiate a period of temporary stress, well known for its effect on the adrenal cortex.[49] With removal of stress, production of adrenocortical hormone might reach a level whereby its beneficial effect could be exerted and a remission induced. It is noteworthy also that this patient first had diarrhea at the time of menarche.

In summary, these collected data all imply that lipophagic granulomatosis is a systemic, acquired disorder, the result of repeated stress from noxious stimuli. Although the noxious agent is not identifiable, the end functional result appears the same as in other similar adaptation diseases, e. g., adrenocortical exhaustion, at the same time raising further the threshold of reaction to injury. As in similar disorders, there may be a selective depletion of certain corticoid fractions that may be responsible for their existence as entities.

Finally, impaired cortical response may result in a disturbance of enzyme equilibrium and distort the normal metabolism of phospholipid. This response is postulated as the basis for a disturbance either in formation of intestinal phospholipid or in its subsequent alteration in the lacteals. As a consequence, fat flocculation in the lacteals and elsewhere would ordinarily result in fat deposition. In such a situation, flocculent fat, being particulate matter, would become blocked by the filtration

48. Selye, H.: Textbook of Endocrinology, Montreal, Acta Endocrinologica, University of Montreal, 1947.

49. Grollman, A.: Essentials of Endocrinology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947.

process of the lymph node barrier and eventuate in lacteal obstruction. At the same time, increasing deposition in the mesenteric and retroperitoneal nodes, the mild foreign body reaction with fibrosis and, still later, flocculation due to retrograde stasis should offer optimal conditions for malabsorption of fat.

SUMMARY

A clinical and pathologic study of 34 collected cases of lipophagic intestinal granulomatosis (Whipple's disease) is presented. Certain resemblances to the collagen diseases and hypoadrenocorticism are emphasized. A new concept of pathogenesis is formulated, based on recent investigations in fat absorption and the physiologic action of the adrenal steroids. Possible future benefit from treatment with the adrenocorticosteroid fractions and pituitary adrenocorticotropic hormone (ACTH) should be borne in mind.

Dr. Nelson F. Young, Department of Biochemistry, Medical College of Virginia, performed the chemical analysis of the lymph nodes.

News and Comment

GENERAL NEWS

First International Congress of Internal Medicine.—The First Congress of the International Society of Internal Medicine will be held in Paris from Sept. 11 to 14, 1950. Among the papers to be presented at this Congress will be "Streptomycin and Neomycin: An Antibiotic Approach to the Chemotherapy of Tuberculosis" by S. A. Waksman, New Brunswick, N. J.; "Recent Advances in Our Knowledge of the Malarial Parasite" by H. E. Shortt, London, England; "Introduction to a New Cholesterol-Degrading Hormone" by A. B. Roy, Allahabad, India; "The Applicability of Hevesy's Method (Erythrocytes Labeled with P^{32} in Physiologic and Clinical Studies of the Circulation)" by G. Nylin, Sweden, and "The Metabolic Effect of Pure ACTH-Protein and ACTH-Peptides in Cases of Rheumatoid Arthritis" by R. Luft, B. Sjögren and C. H. Li, Sweden. Members of the Congress are requested to send in their applications by Aug. 1, 1950. All correspondence concerning the Congress should be addressed to the Organizing Committee of the First International Congress of Internal Medicine: Prof. L. Justin-Besançon, 38, Rue Barbet-de-Jouy, Paris 7e, France.

Book Reviews

Intestinal Intubation. By Meyer O. Cantor, M.D., M.S., F.A.C.S. Price, $7.50. Pp. 333, with 147 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

This finely printed, profusely and beautifully illustrated monograph tells all there is to know about intestinal intubation. There is the history of intubation from the earliest times; the anatomy of the gastrointestinal tract from the standpoint of intubation is described; technic is outlined, and clinical indications are thoroughly discussed. There is a comprehensive bibliography and several indexes.

One wonders, however, whether it is really necessary to have a whole book on every detail of medical and surgical practice. The production of highly specialized monographs no doubt serves a useful purpose, but few men can afford to buy many volumes at current prices. Furthermore, many technical monographs are soon out-of-date as a procedure is improved or loses favor. Be this as it may, the present treatise is undoubtedly the last word in the way of a reference book on the subject of intubation and includes between two covers a great garner of scattered information.

Hemorrhagic Disorders. By Paul M. Aggeler and S. P. Lucia. Price, $10. Pp. 112. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1949.

The current philosophy of so-called audiovisual aids has stimulated the production of a number of books in which a subject is tersely dealt with by means of drawings and diagrams supplemented with brief explanatory legends. The authors of the present volume discuss blood coagulation and hemorrhagic disease by these means. An excellent technical job has been done with beautiful colored drawings and good charts. The essential defect of this method of teaching is, of course, that the legends, from the nature of the medium, must be brief and dogmatic. When one finds under the heading of treatment of a certain disease items 1, 2, 3, tersely set forth, one approaches the cookbook method of "break two eggs, add an ounce of flour, stir," etc. Even in making a cake the skilled touch must be added, and this "cookbook style" which is becoming more and more popular in medical texts seems to the reviewer open to criticism, especially when one is trying to instruct those not already familiar with the subject. With these reservations the book may well be praised; it is full of precise and useful information and is indeed, as its authors define it, a "guide" rather than a full discussion. The supplementary material on therapeutic agents and their use is comprehensive and authoritative.

Transactions of Conference on Factors Regulating Blood Pressure. Price, $2.55. Pp. 280, with 48 illustrations. Josiah Macy, Jr. Foundation, 565 Park Ave., New York 21, 1950.

This collection of papers, which represents the transactions of the Third Conference on Factors Regulating Blood Pressure, held in May 1949, gives the views of two dozen recognized authorities on various phases of the problem of blood pressure. The articles are all interesting and, with the discussion added after each, will stimulate anyone concerned with the subject and bring him fairly well up to date.

Grundlagen zur Erforschung des Alterns. By Paul Matzdorff. Price, 13.50 marks. Pp. 248. Dietrich D. Steinkopff Verlagsbuchhandlung, Einbaumstrasse 2, Frankfurt am Main–Griesheim, Germany, 1948.

The book is divided into a general and a special part. The general part deals with primary aging and is concerned with the processes which are associated regularly with the advance of biologic time and which fall on the descending part of life's curve. Old age is recognized as that period in which deficiencies in these processes become noticeable. The somatic changes, anatomic and functional, furnish valuable information, as well as do the mental changes. The beginning of aging in human beings varies, depending on the point of view. If the social value of the person is contemplated, his efficiency in his calling and in other undertakings is decisive. If resistance to disease or the reaction to therapeutic measures is taken as a criterion, a different timing prevails. One of the great difficulties in judging primary aging is due to the fact that disease may change the "normal" course of aging. A main subdivision of the general part of the book is devoted to the progress of aging and its cause.

The aging of the colloids and of the cells is described in a summary, which starts from a law that everything in nature tends toward an equilibrium. The colloids undergo a decrease in dispersion with liberation of fluid, increase of viscosity and greater tendency toward coagulation. The living cells consist of colloids, the mass of which constantly increases by virtue of ferment activity. These forces of growth counteract the entropy and so prevent aging of the cell. When the energies resulting from the laws of the nucleus-plasma relation interfere with growth, the cell must divide itself or it becomes subject to the laws of entropy and so to aging. The loss of the faculty of cell division is a condition necessary for aging and death. The appearance of fatty deposits further indicates a change of the colloids. This is called "endogenous aging." When external influences also become operative—and the cell's metabolic products act as such an influence—there is a secondary exogenous aging. It is pointed out that the aging of nerve cells and their immediate surroundings shows in that tissue; the nuclei of ganglion cells become denser and pigment deposits appear. The cells and fibers of the neuroglia increase in number. The aging of multicellular tissues manifests itself in a decrease of their water content, first more rapidly, then more slowly. At the same time certain substances are deposited, although not the same in all organs. For these a special designation *"Hortungskoerper"* (storage substances) is proposed. In more advanced multicellular individuals the influence of the nervous system on aging is limited to this: that inactivity leads to more rapid aging.

It is also indicated that some symptoms of aging are associated with the aging of the gonads and regression of their function. But these changes are not the cause of aging. Similarly, there is not sufficient evidence to permit ascribing aging in general to a primary aging of the endocrine glands or to the aging of one of them.

The author further states that the normal aging of the vascular system is seen in distention and fibrous transformation of the walls of arteries, veins and capillaries. It is conceded that consequent interference of nutrition may favor a more rapid aging. Nevertheless, within very wide limits the degree of aging of the tissues does not parallel that of the vessels.

With regard to the causes of aging, it is stated that complete inactivity favors aging of cells. Increasing activity counteracts aging so long as restitution of protoplasm loss is possible. When this no longer possible, aging due to using up of body substance sets in.

An influence of metabolism or intoxication as a causal factor of aging is not supported by adequate evidence, although nutrition seems to exercise some influence on the process of aging. Within certain limits fasting and fever may counteract aging. Heterochronic, synchronic and harmonious aging are outlined. It is emphasized that aging free of disease is rare. Various factors in relation to disease and aging are discussed.

More than half the book is given to the special part and deals first with the bodily changes of age, according to the various system. The changes of the vegetative system, composed of the vegetative nervous system and the endocrine glands, are considered, as is the response to chemical and bacterial exposures. With regard to the autonomous nervous system, an increase in the tonus of the parasympathetic system with age is accepted. Among the features presented under the heading "central nervous system," changes in standing, walking and speech and tremor are included.

The psychic changes of aging are given considerable space. Changes in perception, memory and thinking are treated, among others. A decline in thinking proficiency is seen in the automatization of the thinking processes. Thus, an increase of "no language thinking" in fields to which the person is habituated is noted. It should not be forgotten that the problem of "no language thinking" is beset by great difficulties. Feelings, including, for instance, those of hunger and thirst, are taken into consideration. A variety of psychic phenomena, including conscience, aging of feelings and of the will and changes in character, are outlined. It is regarded of the greatest importance that possibilities for work be found for the aging person, making use of the favorable properties which distinguish advancing age. Indeed, this is accepted as one of the main directives of investigation in geriatrics.

Psychic diseases of age are treated shortly. Perusal of the book impresses one with the difficulties in the investigation of aging. Much interesting material is presented in an interesting manner.

Diseases of the Foot. By Emil D. W. Hauser, M.D. Second edition. Price, $7. Pp. 415, with 195 illustrations. W. B. Saunders Company, 218 Washington Sq., Philadelphia 5, 1950.

Some time ago this reviewer considered another and even larger book on the foot and ankle. At that time he raised the question of whether "topographic" monographs were the best way of dealing with disease. In the case of the foot, for example, there are the obvious surgical and orthopedic problems which have little in common with circulatory disorders or ringworm. Is the orthopedist the man to write about thromboangiitis obliterans, or does not the discussion of that subject belong rather in a book on vascular disease in general? In the present instance, this book, which after all deals mainly with surgical and orthopedic conditions, obviously fills a want, since this is a second edition. It is well printed and illustrated, and there are good bibliographies at the end of each chapter.

Clinical Diagnosis by Laboratory Examination. Second edition. By John A. Kolmer. Pp. 1,212, with 93 illustrations. D. Appleton-Century-Crofts Company, Inc., 726 Broadway, New York 3; 31-32 Bedford St., Strand, London, W.C.2, 1949.

A book embodying the experience of any one like Dr. Kolmer, who has for years developed laboratory diagnosis, cannot fail to be useful. The present volume quickly ran through the first edition and now appears in a recent revision,

but in essentially the same format. All the laboratory tests in common use are described and appraised; there are many good illustrations and useful tables. The one feature which does not appeal to the reviewer is the discussion of a test and the description of technic in two widely separated parts of the book. This leads to some repetition. Some of the brief descriptions of disease which precede discussion of the tests also serve no very useful purpose, as one assumes that the reader is already familiar with the elements of the situation he is investigating.

Food and Facts for the Diabetic. Price, $4. Pp. 113, with 16 illustrations. **Diabetes and Its Treatment.** Price $10. Pp. 326. By J. H. Barach, M.D. Oxford Medical Publications, Oxford University Press, Amen House, Warwick Sq., London, E.C.4, and 114 5th Ave., New York 11; 1949.

The reviewer remembers, perhaps imperfectly, that Dr. William Osler used to tell his students: "Know syphilis and you will know medicine." Today syphilis has given way in importance to other chronic diseases, among them diabetes, and Dr. Barach now can write with complete propriety that "the man who knows diabetes and how to treat it properly will be completely equipped to deal with almost every other of the so-called chronic systemic or nutritional diseases, as they are known in our day." No tissue or organ is immune to the effects of diabetes mellitus.

This book was written not for the scientist nor for the clinical researcher, but for the physician in general medicine. A brief review of the highlights of the history of diabetes is followed by consideration of incidence, etiology and diagnosis. The complications of diabetes and their treatment follow, then prognosis, and finally the treatment of the disease itself; namely, its general management with diet and insulin. This order, although surprising, is understandable, because nearly half the book is devoted to the topic of "General Management," and to insert this large section earlier would have been awkward. The several sections mentioned are profusely illustrated with references to the experience of the author.

The section on "Diets and Daily Menus," designed as it was to spare the physician the necessity of calculating diets, introduces undesirable rigidity, but this is mitigated to some extent by the permissible substitutions shown in separate tables. The amounts of food in the menus are given both by weight in grams and by appropriate household measures. The use of the latter is encouraged; indeed, in Dr. Barach's experience most patients do well on diets that are only relatively accurate, as household measures can be expected to be.

A very useful chapter is the one devoted to the diet and insulin requirements of children.

The section on diets and daily menus, supplemented with a brief comment on the clinical manifestations of diabetes and the nature of the disease, is published separately under the title "Food and Facts for the Diabetic," for use by patients.

Dr. Barach, president of the American Diabetes Association from 1944 to 1946 and chairman of the Metabolism and Endocrinology Study Section of the Research Grants Division of the United States Public Health Service, is associate professor of medicine at the University of Pittsburgh and medical director of the outpatient department of the Pittsburgh Medical Center. He thus has had a large experience with diabetes mellitus and can write with authority. What he has to say is interesting and instructive. The style is unconventional but not displeasing. The book leaves one convinced that its author is a very wise physician.

The Physiological Basis of Medical Practice. By C. H. Best, M.D., D.Sc. and N. B. Taylor, M.D. Price, $11. Pp. 1,330. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

The popularity of this well known text is attested by the fact that this is the fifth edition since the original one appeared in 1937. All have been reprinted several times, the fourth edition in 1945 having been reprinted six times. The present text has been brought completely up to date to include such recent developments as the newer knowledge of the steroids of the adrenal cortex and their application in rheumatoid arthritis, the latest studies of shock and the lower nephron syndrome, Trueta's work on renal circulation and nutritional factors in blood formation.

In the reviewer's experience no book so completely provides the link between the clinician in practice and the interpreter of physiologic mechanisms in the laboratory as does this immensely useful volume. A short description of the gross and microscopic anatomy of the body system being discussed precedes an authoritative review of the physiology. Pathologic changes resulting in disease are then related to the altered physiology so that a rational approach to therapy is suggested to the practitioner. Every internist endowed with a normal amount of intellectual curiosity about the pathologic states he is treating will insist on having this volume in his library, once he has made its acquaintance. The authenticity of the statements, the completeness and discrimination with which the recent medical literature has been surveyed and the understanding of clinical problems by men whose activities are primarily in the laboratory are deeply appreciated by both the old and new friends of Best and Taylor's "Physiological Basis of Medical Practice."

Lehrbuch der inneren Medizin. Volume I. Edited by Helmut Dennig. Pp. 999, with 44 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This volume represents presumably the first half of a new German textbook on internal medicine. The several sections are written by different authors. The section on infectious diseases is by Prof. H. Dennig, of Stuttgart, that on diseases of blood by Prof. H. Schulten, of Cologne, that on diseases of metabolism and internal secretion by Prof. H. Reinwein, of Kiel, that on diseases of bones, joints and musculature by Dr. M. Broglie, of Schleswig, and that on diseases of the mediastinum the respiratory system by Prof. A. Heymer, of Essen-Werden. To come later are sections covering diseases of the heart, the gastrointestinal system, the urinary tract and the nervous system.

The book is well illustrated, and the descriptions of diseases, so far as the reviewer is qualified to determine, are satisfactory. There is no attempt made at documentation, and possibly the more important references could be cited with advantage. The section by Reinwein on diseases of metabolism and internal secretion impresses the reviewer as being especially satisfactory. The section includes discussion of the diseases of the thyroid, the parathyroid, the adrenal glands, the pituitary-diencephalic system, diseases of the islet organ and diseases of metabolism, including gout, porphyrinuria, obesity, lipidosis and the vitamin deficiency states. This is pleasing to the reviewer, who long has maintained that diseases of the endocrine glands and diseases of nutrition are primarily diseases of metabolism. For the reader of German this ought to be a very useful textbook.

Hindu Medicine. By H. R. Zimmer. Price, $4. Pp. 203. Johns Hopkins Press, Homewood, Baltimore 18, 1948.

These lectures, by a great Sanskrit scholar, interpret for the Western reader the Hindu philosophy of medicine. One must say philosophy advisedly, since the system exposed in the Vedas and other Hindu writings is not based on anatomy or pathology but on folklore or other esoteric concepts. Dr. Zimmer writes in a lucid and instructive style, and the reader finds it hard to put down the book. Dr. Edelstein's introduction also is intensely interesting; the account of Zimmer and his work grasps one's attention as much as the lectures themselves.

Electrocardiographic Technique. By Kurt Schnitzer. Price, $3.50. Pp. 96, with 46 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This little book, profusely illustrated with photographs and diagrams, tells in one-two-three order how to handle the various types of electrocardiogram and just how to proceed in taking different leads. Sources of error and pitfalls in operating the machines are discussed. The comment may be made that the expert does not need such a vade mecum, whereas an uninstructed person could hardly be expected to proceed without supervised experience.

Helpful Hints to the Diabetic. By William S. Collens, M.D., and Louis C. Boas, M.D. Price, $3. Pp. 135, with 64 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, Ill., 1949.

This is another book of the diabetic manual type but rather different from most of its predecessors. The outstanding features are the excellent illustrations, many of them in color, picturing, for example, the technic of insulin injection. There are also many useful diagrams concerning the action of the various insulins. All the ordinary things which the diabetic patient needs to know are thoroughly discussed. There are several pages warning persons with diabetes against fraudulent "cures," a warning which certainly can do no harm.

Angina Pectoris and Myocardial Infarction. By Heymen R. Miller, M.D. Pp. 336, with 63 illustrations. Price, $8.75. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

In this interesting monograph the author is especially concerned with the explanation of cardiac pain in terms of the nervous pathways involved. This subject is thoroughly gone into, and one must admire the great number of beautiful anatomic diagrams and dissections of the autonomic pathways. There is a huge bibliography, and the paper and print are excellent. The reviewer does not feel competent to criticize the validity of all of the highly specialized and complex material presented in this book, but it seems a valuable addition to the literature on cardiac pain.

Hematology. By Willis M. Fowler, M.D. Price, $8.50. Pp. 535, with 104 illustrations. New York: Paul B. Hoeber, Inc., 1949.

Dr. Fowler's book on hematology has the virtue of being comprehensive and adequate without being too highly specialized. Hematology has become more complex than ever in the past few years. New syndromes have been described, and new discussions on the classification of cells are afoot. The vogue for bone marrow puncture has added to the complexity of interpretation. Sometimes one feels, in reading the report of a "hematologist," that the author is bogged down

in a mass of verbiage and that what he has to say may be of little help to the physician with a patient. Such "superspecialization" is avoided in this treatise, although what the ordinary physician needs to know is thoroughly discussed.

The book is handsomely printed on fine paper, and the illustrations are excellent.

Clinical Case-Taking. By George R. Herrmann, M.D., Ph. D. Price, $3.50. Pp. 240. St. Louis: The C. V. Mosby Company, 1949.

"Clinical Case-Taking" is an outline of a standard method for the medical interview and the physical examination, organized so as to present an acceptable plan with necessary modifications when symptoms referable to the various systems are encountered. The book is easily read and provides a convenient source of reference for those physicians interested in obtaining a complete medical interview and performing a complete physical examination. Although it considers the semeiology of disease in a logical fashion, it is not a textbook of physical diagnosis. The text is excellent for persons concerned with the practice of clinical medicine, and particularly for medical students and interns.

Cardiovascular Disease. By Louis H. Sigler. Price, $10. Pp. 551, with 149 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

The author has presented in a most interesting manner an adequate discussion of diseases of the heart and vessels. Introductory chapters briefly discuss the etiology of cardiovascular diseases and give a concise review of the anatomy and physiology of the heart. By combining explanation with the clinical findings, symptoms and pathology, the author has made this a most informative and attractive discussion on cardiovascular diseases. Space has been well relegated to the study of heart sounds and the arterial and venous pulse. In a chapter on methods of studying the heart, brief mention is made of the recently developed complicated diagnostic procedures. Methods of treatment are excellently outlined; they include the use of recently introduced drugs.

The author has included a chapter on some of the diseases of the systemic blood vessels. Anticoagulant therapy receives rightful attention here, and also in the treatment of myocardial infarction. Chapters given to the care of patients with cardiovascular disease in pregnancy and to surgical procedures complete the book. The author has used the literature freely, combined with his own experience. The easy readability of this book makes it a worth while contribution to the library of the practicing clinician as well as to that of the medical student.

CORRECTION

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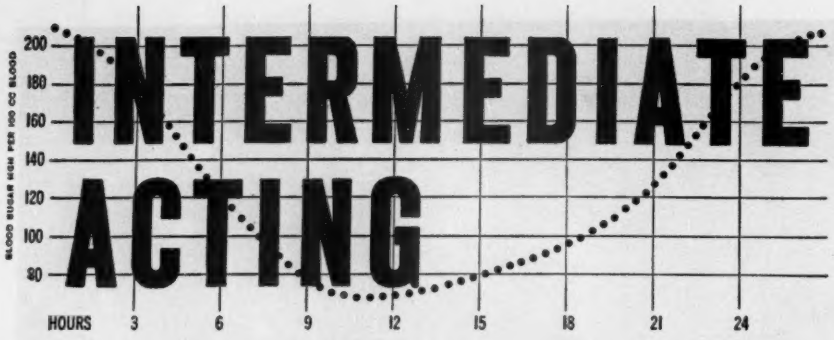

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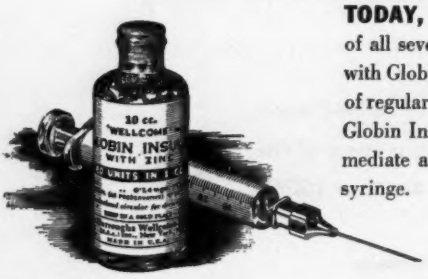

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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